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TETANY IN NEWBORN INFANTS

RELATION TO PHYSIOLOGIC HYPOPARATHYROIDISM

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RECENT experience has made it apparent that tetany is a not infrequent disorder of the newborn period; indeed, with the diminution in the number of cases in later infancy now that vitamin D preparations are so widely used, tetany of the newborn may well become the most frequent form seen by the pediatrician.

Any convulsive disorder in the newborn infant is of grave significance. Since there is available an effective agent for the treatment of tetany, namely calcium, it is essential that this condition when present should be promptly recognized. There are, however, other aspects of this subject which lend it more general significance. The occurrence of tetany in the newborn infant throws interesting light on the complicated adjustments which the newborn infant must make when he is separated from the maternal circulation, and it makes doubtful a common practice in the care of the newborn, namely, the early use of cow's milk feeding.

Tetany in the newborn was first mentioned in 1913 by Kehrer,[1] a Swiss physician, who described a group of newborn infants with convulsions, flexor spasms of the extremities, and positive facial and Trousseau reactions. Rapid improvement followed the administration of calcium. Whether or not Kehrer's patients actually had tetany will never be known, since the clinical manifestations in this condition are not sufficiently definite for a diagnosis to be made, and blood calcium determinations were, of course, not done. Kehrer's report was widely discussed, and it was generally agreed by competent observers that tetany does not occur in the newborn infant. It was not until almost twenty years later that reports of this condition reappeared in the literature.

In 1931 Bass and Karelitz[2] described three newborn infants with symptoms similar to those described by Kehrer, and in whom dramatic

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improvement followed the intravenous injection of calcium gluconate. The serum calcium was determined in only one of their patients, and this showed 8.5 mg. per cent, a value which can hardly be accepted as tetanic; nevertheless, their report served to stimulate interest in this subject and within a few years there appeared in the American pediatric journals a large number of case reports about which there can be little doubt. There have been reported up to the present twenty-seven cases of tetany in the newborn which can be considered reliable, and I am sure that many more have been observed which have not been reported.

The clinical features of tetany in the newborn differ in no essential respect from those in later infancy. The condition may be symptomless, the diagnosis being made accidentally by examination of the blood for calcium. We have observed one such instance. Or there may be merely an exaggerated facial or peroneal reflex.

Of the frank clinical manifestations, convulsions and twitchings are by far the most common. These are in no way characteristic and cannot be distinguished from convulsions and twitchings due to other conditions. Laryngospasm and carpopedal spasm are rare and when present not easy to interpret. A heightened response to sensory stimuli such as loud noises or jarring of the crib is frequently observed in the newborn infant as well as in the older infant with tetany.

On the whole one may say that the clinical picture in tetany of the newborn is not specific. Whenever convulsions, twitchings, abnormal hypersensitivity, exaggerated facial and peroneal reflexes occur, the diagnosis should be suspected and a determination of the serum calcium made.

Rickets, clinically or roentgenologically, is not observed in these patients. The blood shows a reduction in the serum calcium below 8 mg. and often below 7 mg. The serum phosphorus is usually elevated but may remain within normal limits. The serum phosphatase, unlike that in the tetany of later infancy, is unchanged.

The parents are ordinarily healthy, and in at least two of the reported cases the mothers received vitamin D supplements during part of the pregnancy.

The prognosis is good. The two deaths out of the twenty-seven reported cases were due to associated cerebral hemorrhage. A permanent cure can be promptly effected by the administration of calcium. Unless convulsions are severe or continuous, calcium may be given by mouth as the chloride (well diluted), lactate, bromide, or gluconate. When a quick result seems desirable, calcium should be given intravenously, preferably as the gluconate. Intramuscular injection is inadvisable, since calcification of the subcutaneous tissues with abscess formation is a not infrequent occurrence. There is no need for the use of parathormone in this condition. The dosage is difficult to gauge; there is danger of either underdosage or overdosage.

PATHOGENESIS OF TETANY OF THE NEWBORN

The forms in which tetany is known to occur clinically or experimentally may be divided into two groups depending on whether or not the serum calcium is reduced (Table I). Tetany without a reduction in the serum calcium, referred to in Table I as "normocalcemic" tetany, occurs under circumstances where the activity of the serum calcium, but not the total amount, is believed to be reduced. This group need not be considered here since the serum calcium in tetany of the newborn is reduced. The diagnostic criterion in normocalcemic tetany is a change in the reaction to galvanic stimulation.

Hypocalcemic tetany may result from parathyroid deficiency, from the injection or ingestion of phosphates, from vitamin D deficiency, or from disease of the upper intestinal tract. There is no reason to believe that intestinal tract disease exists in the newborn, and we may safely discard this as a possible mechanism in tetany of the newborn.

TABLE I

FORMS OF TETANY

Normocalcemic	Hypocalcemic
1. Alkalosis	1. Vitamin D deficiency
a. Gastric	2. Parathyroid deficiency
b. Bicarbonate	3. Phosphate
c. Hyperpnea	4. Due to upper intestinal disease
2. Citrate	
3. Oxalate	

Parathyroid Deficiency.—Hemorrhage into the parathyroids, as a mechanism leading to tetany in older infants, was suggested thirty years ago by Yanase,[3] a pupil of Escherich's, and he was able to demonstrate bleeding into the parathyroid glands in a considerable proportion of newborn infants. It was found, however, that such hemorrhages occurred as frequently in normal infants as in those in whom tetany was suspected.[4] Fresh and old hemorrhages, blood cysts, and blood pigment are frequent in the parathyroids of infants dying of the most varied diseases, occurring in about 30 per cent of the autopsy material. Some of the hemorrhages occur during the neonatal period and some later. In the newborn infant with tetany described by Guild[5] no changes in the parathyroid glands were observed at autopsy.

Parathyroid hemorrhage, as a factor leading to tetany during the neonatal period, seems unlikely from the behavior of the serum calcium during the first ten days of life. As illustrated in Chart 1, there is a trend during this period toward a lowering of the serum calcium which is general. At birth (cord blood) the serum calcium is high, averaging 11 mg. per 100 c.c. From the third to the fifth day the serum calcium drops to an average value of 9.76 mg. after which it rises to 10.36 mg. by the sixth to the tenth day. In only three of the sixty-one cases was

the serum calcium as high as the average value for the placental serum. At the same time there is a gradual elevation of the serum phosphorus.

If tetany of the newborn were due to hemorrhage into the parathyroids, one would hardly anticipate a general depression of the serum calcium content but would expect, instead, a lowering in an occasional infant, with the general level remaining unchanged.

It is possible, however, that parathyroid hypofunction, on a basis other than hemorrhage, may be a factor in this form of tetany. During pregnancy there is histologic evidence of hyperactivity of the maternal parathyroid glands,[6] and the blood of pregnant women contains increased amounts of a substance which behaves pharmacologically like parathyroid hormone.[7] It is conceivable that parathyroid activity in the fetus is in abeyance in response to the maternal overactivity. If this hypothesis is correct, one would expect a fall in the serum calcium of the newborn infant shortly after birth in the interval between the dis-

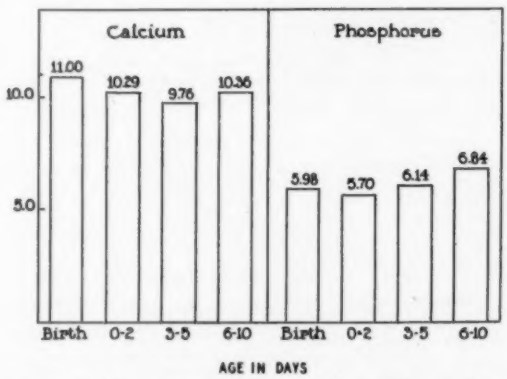

Chart 1.—The serum calcium and serum inorganic phosphorus during the first ten days of life.

appearance of maternal parathyroid hormone from the newborn infant and the assumption of normal function by the infant's own parathyroids. There may be an analogy here to the hormonal interchange between mother and fetus which occurs in diabetes,[8] where the fetal islands of Langerhans become enlarged and hyperactive in response to the maternal hyperglycemia and symptoms of hyperinsulinism in the newborn may occur.

The possibility of an exchange of parathyroid hormone between mother and fetus was investigated a number of years ago by Hoskins and Snyder.[9] They injected large amounts of parathyroid extract into dog fetuses in utero and observed a rise in the calcium content of the fetal serum. The calcium content of the maternal serum, however, remained unchanged. On the other hand, injection of parathyroid extract into the mother resulted in a rise in both the maternal and the fetal

values. From these studies they concluded that parathyroid hormone does not pass from fetus to mother; but whether it passes from mother to fetus remained undecided since, they thought, the fetal hypercalcemia following maternal injection may have been due to either passage of parathyroid hormone from mother to fetus or may have been simply a response to the maternal hypercalcemia.

It is known now, however, that the fetal serum calcium varies independently of the maternal serum calcium,[10] so that it seems reasonable to assume from those experiments that parathormone may pass from mother to fetus.

The possibility that parathyroid deficiency in the newborn may result from withdrawal of the maternal supply of parathormone was investigated by comparing the serum calcium content of placental blood with that of blood withdrawn from the infant two to four hours after birth. The results in the seven patients studied are illustrated in Chart

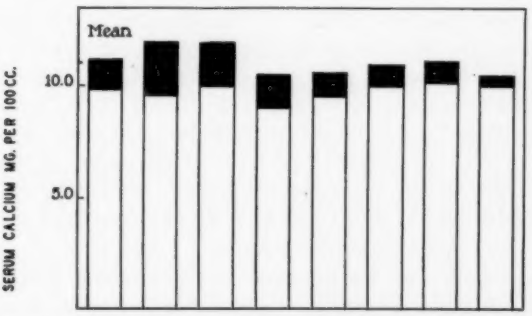

Chart 2.—Comparison of the placental serum calcium and the serum calcium of infants two to four hours after birth. The total height of the columns represents the placental serum calcium, the black areas the amount of reduction.

2. Within this short space of time there occurred regularly a fall in the serum calcium varying from 0.8 to 2.0 mg. per 100 c.c. and averaging 1.56 mg. It is difficult to explain these findings on any basis other than parathyroid deficiency.

Of interest in this connection is the reduction in the urinary excretion of phosphorus in the newborn infant[11] since this is one of the most striking phenomena observed in hypoparathyroidism.[12] There is an appreciable but small amount of phosphorus in the urine of the newborn infant during the first three days of life. During the second three days of life the amount falls, and during the third three days there is a slight increase, the amount, however, not reaching the initial value.

Relation to Phosphate Tetany.—Hypocalcemic tetany may be induced in dogs by the intravenous injection of neutral or alkaline phosphate,[13] and it is also possible to bring about tetany in dogs and in infants by the oral administration of phosphate.[14] Rohmer and Woringer[15] showed, however, that whereas hypocalcemia may be readily induced in

infants with rickets, the ingestion of phosphate has no marked effect on normal infants, and their observation has been confirmed by other workers.[16]

Another group of individuals who are sensitive to phosphate ingestion, in the sense of developing hypocalcemia, are the parathyroid deficient. Parathyroidectomized rats can be kept free from tetany by reduction of the phosphorus in the diet;[17] and tetany can be induced in such animals at will by adding phosphorus to an otherwise optimal ration. The same series of events has been observed in patients with parathyroid insufficiency, and low phosphorus diets are consequently used therapeutically in this condition.[18]

We see, then, that two groups of individuals are susceptible to phosphate ingestion, the vitamin D deficient and the parathyroid deficient.

There is some reason to suspect that phosphate may be a factor in the pathogenesis of tetany of the newborn. During the first few days of life little if any food is taken. Cavins[19] has shown that rachitic rats readily acquire tetany on fasting, and the tetany in his animals has been attributed to the endogenous release of phosphorus from the tissues during the fast. Indeed it has been possible to induce tetany in rachitic rats by the addition of phosphate to their diets.[20]

The mechanism by which phosphate leads to hypocalcemia is not entirely clear. The most plausible explanation seems to be that phosphate removes calcium from the body fluids by combining with it to form insoluble salts in the lower part of the intestinal tract, thereby preventing the reabsorption of calcium.[21]

The susceptibility of the newborn to phosphate is indicated by the striking fall in the serum calcium of newborn infants following the ingestion of relatively small amounts of phosphate. A standardized solution of sodium phosphate was fed to healthy newborn infants by nasal catheter after removal of the gastric contents. Blood for determination of the serum calcium and phosphorus was drawn immediately before and two hours after the administration of phosphate.

The findings illustrated in Chart 3 indicate an increased susceptibility on the part of newborn infants to the ingestion of phosphate. According to Klercker and Odin,[22] who worked with rachitic, that is sensitive, infants, the minimum dose capable of affecting the serum calcium content of older infants is 160 mg. per kilogram of body weight. In the newborn, amounts as small as 31 mg. produced an appreciable fall.

Relation to Vitamin D Deficiency.—The only form of tetany known to occur in infants after the neonatal period is that due to a deficiency of sunlight or of vitamin D. The infant is born without any reserve supply of vitamin D. This has been demonstrated by both Hess and Weinstock[23] and Toverud and Ender,[24] who found little or no vitamin D in the livers of newborn infants. Nevertheless, disease due to a deficiency of vitamin D is rare in the newborn and has been observed only in China

in the offspring of mothers with osteomalacia. Toverud and Ender assumed that the vitamin D content of the newborn infant's liver is dependent on the maternal diet, but there is no evidence to corroborate this assumption. It would certainly be unlikely (but not, of course, impossible) that all the mothers studied by them and by Hess were vita-

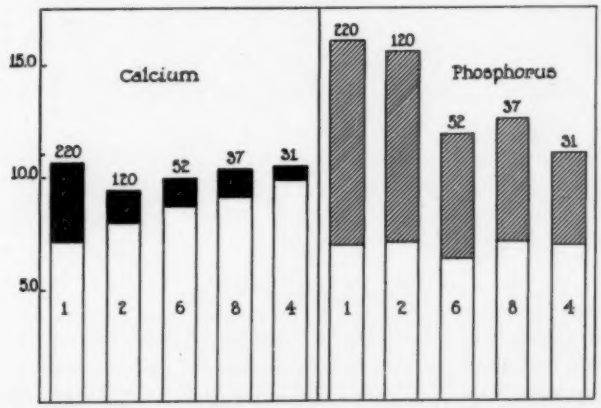

Chart 3.—The effect of ingested phosphorus on the serum calcium and serum inorganic phosphorus of newborn infants. Numerals above the columns indicate dosage of phosphorus in milligrams per kilogram of body weight; numerals inside the columns indicate number of cases.

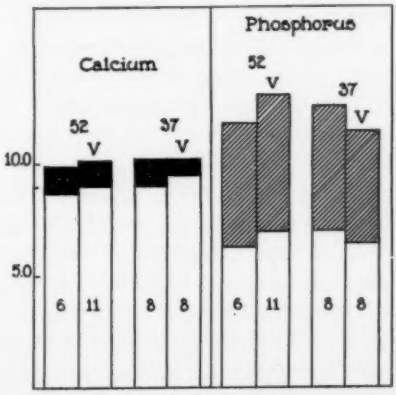

Chart 4.—The effect of vitamin D on the fall in serum calcium and on the rise in serum inorganic phosphorus of newborn infants after the ingestion of phosphorus. In each double column, the column at the left represents control experiments without viosterol, column at right represents experiments with viosterol, *V*. Numerals above the columns indicate the amount of phosphorus given, numerals within the columns the number of cases.

min D deficient. It may be mentioned here again that the mothers of at least two of the newborn infants with tetany received vitamin D supplements during a considerable part of the pregnancy.

In order to determine whether the heightened rsponse of newborn infants to the ingestion of phosphate is dependent on a deficiency of vita-

min D, viosterol was given to a series of newborn infants, and their reaction to the ingestion of phosphate was then tested as described above.

The results are illustrated in Chart 4. Despite the large doses used—30 to 40 drops of viosterol, equal to 6,700 to 8,900 units of vitamin D, for seven to eight days—the response of the serum calcium to phosphate ingestion was not significantly altered. The failure of vitamin D to influence the reduction in serum calcium following phosphate ingestion is strong evidence against the viewpoint that vitamin D deficiency is a factor in the tetany of the newborn.

A striking feature of tetany in the newborn is the curative effect of calcium salts. This is not true of the vitamin D deficiency tetany in older infants in whom calcium salts have at best a palliative effect and are not infrequently without any influence.

DISCUSSION

It seems likely that tetany in the newborn is dependent on a temporary hypofunction of the parathyroid glands. As evidence for this are three groups of observations: (1) the abrupt drop in the serum calcium content within a few hours after birth, (2) the small amount of phosphorus excreted in the urine, and (3) the exaggerated response of the serum calcium to the ingestion of phosphate. That vitamin D plays no part in the pathogenesis of tetany of the newborn is indicated (1) by the failure of vitamin D to modify significantly the drop in the serum calcium following the oral ingestion of phosphate and (2) by the fact that cure follows the administration of calcium in tetany of the newborn, whereas calcium has only a temporary, palliative effect in the vitamin D deficiency tetany of older infants.

Physiologic Hypoparathyroidism.—There exists, then, in the newborn infant, a physiologic hypofunction of the parathyroid glands. This may be classified with the physiologic dehydration and physiologic jaundice of newborn infants and represents a phase in the complex adjustments made necessary by the transfer from intrauterine to extrauterine life.

We do not believe, however, that the physiologic hypoparathyroidism of the newborn is ordinarily sufficient, in itself, to explain the occurrence of tetany of the newborn. It is probable that in this condition, just as in the vitamin D deficiency of older infants, there is usually, but not necessarily always, a second exciting factor or mechanism. But before going on to discuss this second mechanism I should like to call your attention to certain unusual features of tetany of the newborn.

It is well known that tetany of later infancy is much more common in negro than in white infants. In tetany of the newborn, however, there are no reports whatsoever of cases in negro infants. Unusual, too, is the large number of cases in private patients, fully half of the reports of

newborn tetany being in private practice. Tetany in older infants is largely a social disease, being observed much more often in clinic practice.

An interesting feature is the relatively large number of cases observed since 1933. Though tetany of the newborn had been previously described and fairly widely discussed, it is only within the past few years that cases have been observed with any frequency. Another curious aspect of this condition is the fact that case reports are entirely limited to America, no reports having appeared in the foreign literature since 1930. There are a number of papers on tetany during early life and a review of the American reports on tetany of the newborn, but the youngest patient mentioned in the foreign literature was an infant fifteen days old. It appears that tetany of the newborn is an American disease.

The second mechanism, which I mentioned a few moments ago, is phosphate. There is considerable evidence to indicate that both parathyroid deficiency and vitamin D deficiency lead to an instability of the serum calcium and that the hypocalcemia results from phosphate, either endogenously released during the physiologic starvation of the newborn, or, what is probably more important in the newborn, ingested from without in cow's milk.

Within recent years the use of cow's milk supplements in the feeding of the newborn infants has become widespread. The tetanogenic effect of cow's milk on older infants has been known for a number of years and has been widely discussed, particularly in the German and the Scandinavian literature. Infantile tetany is much more common in artificially fed than in breast-fed infants. This is not true of rickets which occurs with equal frequency in both groups. Finkelstein[25] has shown that an improvement in the electrical reactions can be induced in artificially fed infants with tetany solely by the withdrawal of milk and that the tetanic electrical reactions reappear on the reintroduction of cow's milk into the diet. He has also seen the symptoms and electrical reactions of tetany disappear when a tetanic infant is fed human milk instead of cow's milk, and it is still the general practice in Germany to remove cow's milk from the diet of infants with tetany.

The tetanogenic property of cow's milk has been attributed to its high content of phosphate. Cow's milk contains about six times as much phosphorus as does human milk, and the high phosphorus content is only partly balanced by the high calcium content. An ounce of cow's milk contains about 30 mg. of phosphorus. You will recall that a single dose of 31 mg. of phosphorus per kilogram of body weight causes an appreciable drop in the serum calcium. Furthermore, human milk contains more lactose than cow's milk and lactose has been shown to favor the absorption of calcium.

The extra phosphorus ingested in cow's milk may well be the second mechanism in the pathogenesis of tetany of the newborn just as it often

is in the tetany of older infants. This would account for the recent increase in cases, particularly in America, and for the more frequent occurrence of the condition in private patients, who are more likely than ward patients to receive the added attention of early supplementary feeding.

SUMMARY

A physiologic hypoparathyroidism occurs in newborn infants analogous to physiologic dehydration and physiological jaundice.

That the tetany of newborn infants results from hypoparathyroidism is indicated by (1) the abrupt fall in serum calcium within twenty-four hours after birth, (2) the low urinary phosphorus content, and (3) the marked response to phosphate ingestion.

That tetany in the newborn is not related to vitamin D deficiency is indicated by (1) the failure of large doses of vitamin D to influence the fall in serum calcium following phosphate ingestion and (2) the prompt cure with calcium salts.

A second mechanism leading to tetany of the newborn is phosphate, either released endogenously during the physiologic starvation, or, what is probably more likely, ingested from without in cow's milk.

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EMPYEMA IN CHILDREN

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THIS report is based upon sixty cases of empyema in children less than 12 years of age observed during the past eight years at the San Francisco and University of California Hospitals. It is prompted by recent experiences which have demonstrated that the diagnosis and treatment of this disease are still far from satisfactory. The following case histories illustrate these points.

CASE 1.—C. Z., an 18-month-old white female, was admitted to the University of California Hospital after a five-month stay in another hospital. She had been well until six months previously, at which time she developed pneumonia. In spite of the prolongation of cough and dyspnea, with occasional cyanosis and a persistent elevation of temperature, the patient had been discharged home one month before entry here.

Physical examination revealed a thin, chronically ill, irritable, dyspneic child. There were prominent superficial thoracic veins, limited expansion, impaired breath sounds, and flatness over the left lower chest. The mediastinal structures were displaced to the right. The fingers and toes were clubbed.

Aspiration in the eighth left interspace yielded 120 c.c. of thick green pus, which on culture showed a Type I pneumococcus. Tube drainage was instituted a few days later, and siphon drainage and irrigation with Dakin's solution were carried out. The patient was discharged well on the thirty-seventh postoperative day. When seen several months later, she had gained considerable weight and the clubbing was hardly noticeable.

COMMENT

This case illustrates the failure to suspect empyema in spite of the continuation of symptoms following pneumonia. Adequate drainage resulted in a prompt cure and marked regression of the clubbing of the fingers.

CASE 2.—D. L., a white male, 6 years of age, had influenza six months previously. At this time he developed acute appendicitis, and at operation a gangrenous appendix was removed and drainage instituted. One week postoperatively he developed pneumonia, followed by an empyema on the left side. He was immediately treated by thoracotomy and tube drainage without any previous effort at closed drainage. He remained in the hospital for three weeks and in bed at home for two months. The tube remained in the chest all this time, and no cleansing was done. The child remained weak, did not develop physically, and the chest sinus persisted. There were no respiratory symptoms.

Physical examination showed a pale, undernourished boy, with a draining sinus about 7 cm. long in the seventh left interspace at the postaxillary line. There were increased resonance and fremitus over the right chest. Over the left lower lung there were limited expansion, impaired resonance, and diminished breath sounds. The

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left diaphragm was elevated and its excursion limited. There was no apparent mediastinal shift. At the site of a healed McBurney's scar was an incisional hernia. Roentgen examination showed an osteomyelitis of the seventh and eighth ribs.

Under gas and oxygen anesthesia the seventh and eighth ribs were resected, the chronic granulation tissue in the depth of the empyema cavity was curetted away, and the wound then packed with 2 per cent argyrol gauze. The wound was dressed and repacked daily for one week, after which time the boy was discharged in excellent condition.

COMMENT

Immediate open drainage of an empyema during the active stage of pneumonia is definitely contraindicated. Allowing a tube to remain in the chest for almost three months is never justified. This case illustrates one of the causes for a persisting sinus, i.e., osteomyelitis of the ribs.

Table I lists the total number of pneumonia cases seen during the period 1928 to 1936, inclusive.

TABLE I

COMPARISON OF THE PNEUMONIA AND EMPYEMA INCIDENCE AND MORTALITY

YEAR	PNEUMONIA		EMPYEMA	
	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY
1928-29	107	10	8	0
1929-30	65	8	10	0
1930-31	66	5	5	0
1931-32	65	6	5	1
1932-33	69	7	5	1
1933-34	80	5	10	1
1934-35	66	3	5	0
1935-36	111	11	12	2
Total	629	55 (8.7%)	60	5 (8.3%)

In 629 cases of pneumonia in children up to 12 years of age, there was a mortality of 8.7 per cent. The incidence of empyema was 0.9 per cent, which approximates the finding of Pemberthy and Benson,[1] who in 5,868 pneumonia patients found 0.7 per cent developed empyema as a complication requiring surgical drainage. Our empyema mortality in sixty cases was five (8.3 per cent). This series lends some support to the idea expressed that "the type of virulence of the pneumonia preceding the empyema is the most important factor in determining the mortality rate of empyema in a given series treated over a period of years."

TABLE II

DISTRIBUTION OF EMPYEMA CASES AND TYPE OF TREATMENT

AGE (YEARS)	NO. OF CASES	SEX		TREATMENT			MORTALITY
		MALE	FEMALE	ASPIRATION	CLOSED TUBE	RIB RESECTION	
0-1	6	5	1	1	1	4	1
1-2	6	3	3	1	1	4	0
2-5	16	9	7	4	5	7	1
Over 5	32	19	13	3	6	23	3
Total	60	36	24	9	13	38	5

The diseases preceding the empyema in this group were lobar pneumonia in fifty-one cases, bronchopneumonia in five instances, measles twice, influenza in one case, and one patient with rupture of an extrapleural abscess into the thorax. In this series thirty-six cases occurred in males. The left pleural cavity was involved in thirty-two cases. Twelve patients were less than 2 years of age. This small group, however, does not show the higher mortality rate in infancy reported in most of the larger series.

TABLE III

LIST OF CAUSATIVE ORGANISMS IN EMPYEMA

ORGANISM	NO. OF CASES	MORTALITY	ORGANISM	NO. OF CASES	MORTALITY
Strep. hemolyticus	8	1	Pneum. IV and *Staph. aureus*	1	1
Staph. aureus	3		*Strep. hemolyticus* and *Strep. viridans*	1	
Pneum. (undetermined)	5		Pneum. IV and *Staph. aureus*	2	1
Pneum. Type I	10	1	*B. coli*	1	
Pneum. Type III	5		*B. coli* and Pneum. I	1	
Pneum. Type IV	7		*B. coli* and *Strep. hemolyticus*	1	
Pneum. Type V	4		*Strep. viridans*	1	
Pneum. Type XIV	1				
Pneum. Type XXIII	1				
Strep. hemolyticus and *Staph. aureus*	2	1			

Many organisms may cause empyema, as shown in Table III. It is evident that the majority of cases are caused by a pneumococcus or hemolytic streptococcus. In streptococcic empyema the fluid is likely to form early during the course of the pneumonia, is present in greater quantity, and is thinner and contains much less fibrin than in the pneumococcal type. In the latter case the pus is thick, with considerable fibrin, and becomes walled off more quickly than the streptococcus. This walling off process allows the lung to become fixed to the chest wall and stabilizes the mediastinum. This is important before open drainage is instituted.

In order to prevent the serious results of a chronic empyema early diagnosis is essential. In our group the duration before therapy ranged from two days to one year, averaging approximately twenty-nine days. If the temperature does not subside after an attack of pneumonia or if the attack is unduly prolonged, empyema must always be considered. The physical findings reveal decreased expansion on the affected side and later bulging, diminished or absent breath sounds and fremitus, impaired percussion note, and displacement of the heart to the opposite side. This latter sign may not occur even with a fairly large effusion (Figs. 1 and 2), and in an occasional case the trachea may be pulled over to the affected side. The probable explanation for this is that with the accumulation of fluid the respiratory movement of the lung is de-

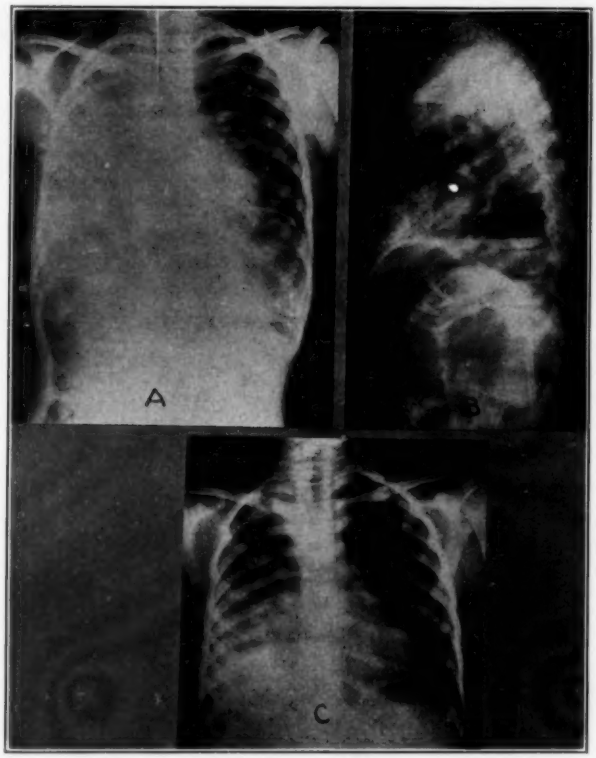

Fig. 1.—*A*. E.P., March 8, 1937, generalized empyema. Note heart and mediastinum not displaced to the opposite side. *B*. March 19, 1937. Tube pressing on diaphragm. Patient complained of shoulder pain. *C*. April 7, 1937. Tube removed. Note shadow at mesial aspect of the right apex. (Azygos lobe; pneumonia.)

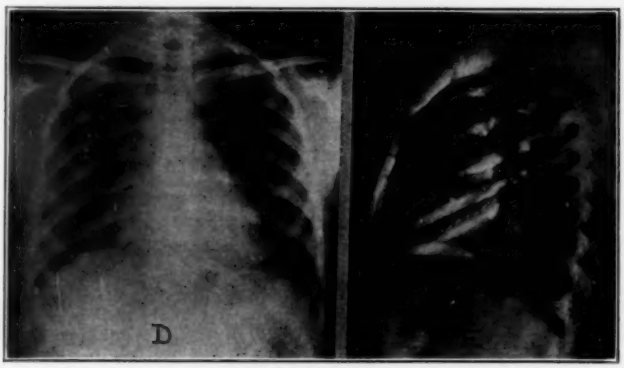

Fig. 1.—*D*. E.P., Jan. 6, 1938. Eight months later, showing final recovery. Note that the shadow at the mesial aspect of the right apex has entirely cleared. *E*. Lateral view of previous film.

creased and there may result from both the compression and the air absorption in the alveoli an atelectasis of the lung on the affected side, which counteracts the effect of the effusion.

Fluoroscopic and roentgenographic examination should never be omitted, as they aid in localizing interlobar and encapsulated collections of fluid. A lateral film is indispensable, as it may show a fluid level that cannot be visualized in the anteroposterior view, particularly when the fluid collection is situated behind the heart shadow. Explora-

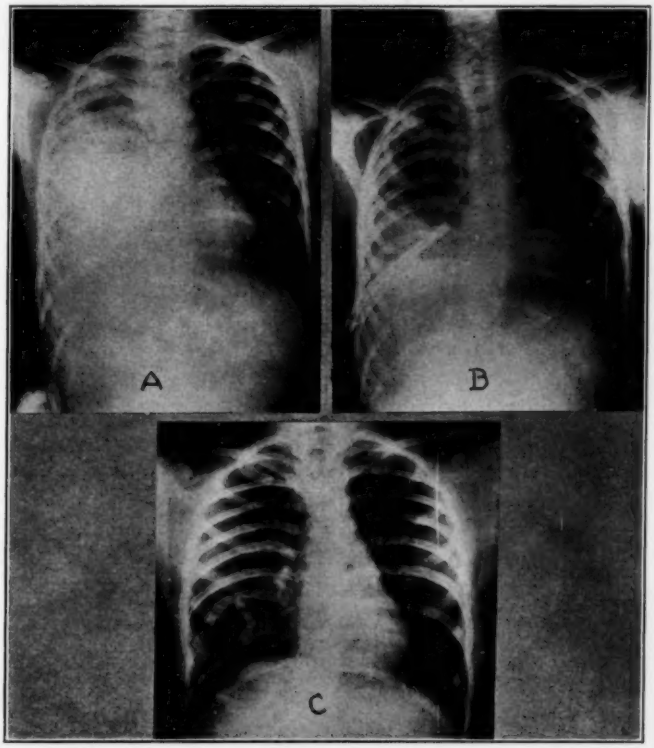

Fig. 2.—*A*. C.H., Dec. 23, 1936. Massive effusion on right side without displacement of the mediastinal structures. *B*. Dec. 31, 1936. Tube drainage instituted but proved inadequate. *C*. Dec. 2, 1937. Approximately one year after rib resection; complete healing.

tion of the chest with a needle after the situation of the fluid has been determined confirms the diagnosis. The character of the pus, smear, and culture aids in determining the further course of treatment.

The two principles to be borne in mind in any form of treatment of empyema are thorough drainage of the chest as quickly as is consistent with the child's general condition and obliteration of the cavity by re-expansion of the lung. There are practically no cases of empyema that require major surgical procedures as an emergency measure during the

acute phase of the disease. Since the vital capacity in an infant is small and the mediastinal structures are not as fixed as in the adult, a moderate, rather rapid collection of fluid in the pleural cavity can seriously embarrass respiration and circulation and result in considerable dyspnea and cyanosis. Aspiration in such cases may be a lifesaving measure. The fluid should be removed slowly, and it must be remembered that a too complete removal may lead to serious symptoms and even death. No open drainage should ever be done during the active stage of the pneumonia. In the absence of protective adhesions an open thoracotomy will result in an inrush of air which will greatly diminish an already greatly reduced vital capacity and reserve air and may prove fatal. In such cases repeated aspirations or closed tube drainage should be carried out. Needle aspirations with air replacements have been unsatisfactory in our hands. The constitutional symptoms persisted longer and re-expansion of the collapsed lung seemed to be delayed with this method. We believe that tube drainage is preferable to multiple aspirations because it gives continuous drainage as opposed to an intermittent type and definitely shortens the period of hospitalization. Nine cases in our series were cured by thoracentesis alone, with an average hospital stay of sixty-three days. In thirteen instances tube drainage was carried out, the average hospitalization period being fifty-six days. This included one case in which repeated aspirations had been tried first. With closed tube drainage a large catheter, preferably 22 F., should be used. We have employed continuous suction or tidal irrigations with normal saline or Dakin's solution, depending on the individual case. A catheter introduced for drainage should not be left in place longer than two to three weeks, at the most. When the temperature has returned to normal, the signs of toxicity have disappeared, the drainage fluid no longer is purulent, and the cavity holds less than 15 c.c., the tube should be removed. If, with closed drainage, recovery is not proceeding satisfactorily, that is to say, the pus continues to accumulate, the cavity is not steadily diminishing in size, and the lung is not beginning to re-expand, it is distinctly advisable to perform open drainage. Otherwise a chronic empyema may develop. In our series thirty-eight cases were treated by rib resection, with an average hospitalization period of sixty-seven days. However, this is not a true reflection of this method of therapy, since fifteen cases had multiple thoracenteses and twelve had closed tube drainage previously, and the time required for these procedures is included in the above hospitalization figure.

Empyema following rupture of an abscess of the lung is a distinct entity. The early distinguishing clinical features are severe, localized, and persistent chest pain, with evidence of marked toxicity. The sputum may become diminished or absent, and there are signs of fluid and air in the pleural cavity. Therapy consists of the immediate institution

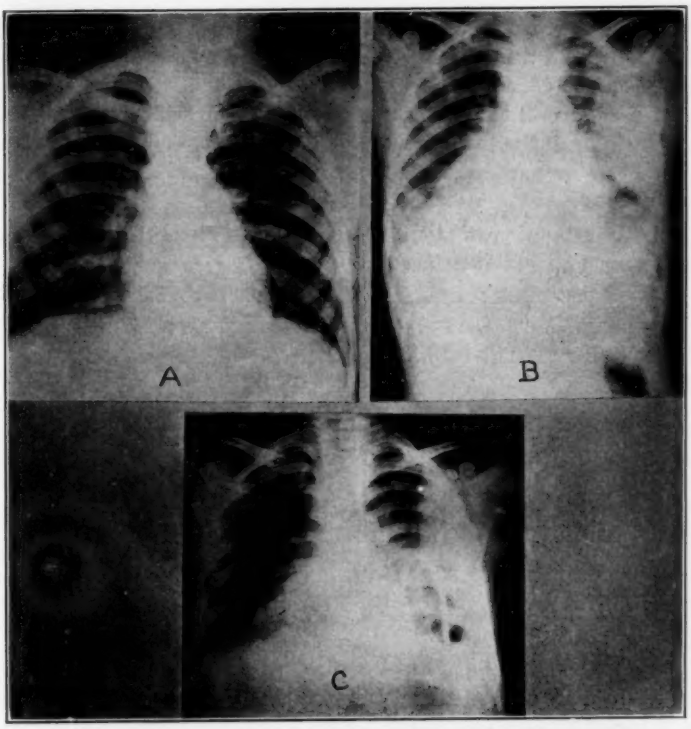

Fig. 3.—*A.* D.McK. Jan. 2, 1937. Patient entered because of congenital genito-urinary condition. Preoperative film of the chest. *B.* Feb. 12, 1937. D. McK. developed pneumonia following operation. Film shows a shadow in the left axillary region and a density at the right cardiac angle. Aspiration revealed pus at this area. *C.* March 2, 1937. Drainage tube in the mesial empyema cavity on the left. The lateral pocket was not touched. The shadow on the right still persists.

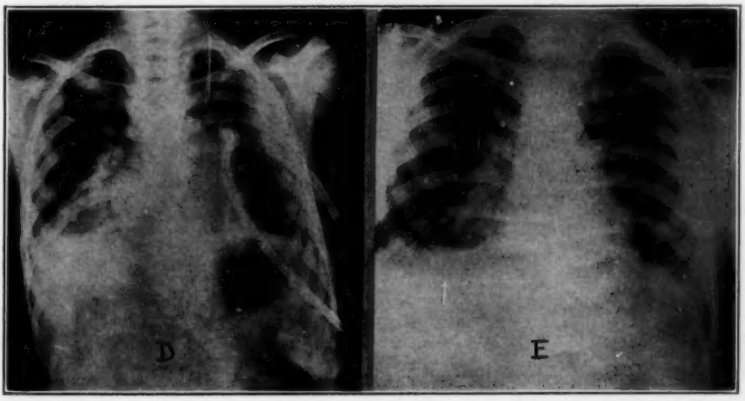

Fig. 3.—*D.* D. McK., March 5, 1937. Film shows two tubes in place in the loculated empyema cavities on the left. Temperature continued. Pus aspirated from the right side and tube drainage instituted later. *E.* April 1, 1937. Loculated empyemas entirely cleared. Lungs re-expanded. Patient perfectly well.

of tube drainage, usually for a period of about five to seven days. This allows the mediastinum to become fixed, and then, after improvement in the patient's general condition, open operation should be performed. Resection of several ribs is usually necessary to provide adequate drainage. Dakin drainage tubes are inserted, and the wound in the chest wall is kept open by gauze packing. The wound is washed and the tubes changed daily.

To aid re-expansion of the lung following treatment of an empyema, blow bottles or wind instruments are extremely useful. An empyema

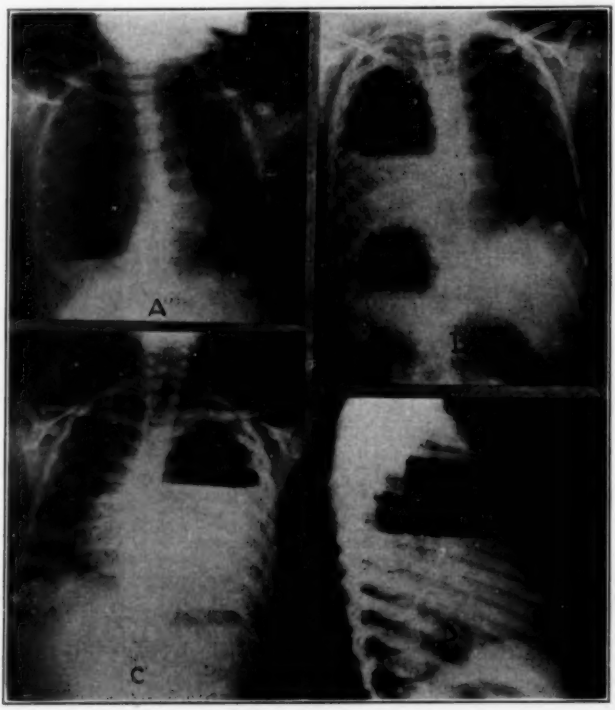

Fig. 4.—*A*. D.E., June 20, 1937. Patient had whooping cough followed by bronchopneumonia and developed slight amount of fluid on the right side. Aspiration yielded 35 c.c. of straw colored fluid. *B*. July 23, 1937. Fluid increased on right side, with marked constitutional symptoms. Tube drainage was instituted on the outside. Tube was left in for only one week. *C*. Sept. 15, 1937. Film taken when patient entered University of California Hospital shows much fluid on the left side, with displacement of the mediastinal structures to the right. *D*. Lateral view of previous film.

is cured only when the cavity is obliterated and the lung is once more in apposition to the chest wall. Failure of an empyema to improve should make one consider: (1) inadequate drainage and failure to obliterate the cavity; (2) persistent bronchial fistula; (3) multiple loculations (Fig. 3); (4) foreign body; (5) osteomyelitis of the rib, or (6) a tuberculous infection.

Brief mention should be made about the use of sulfanilamide in hemolytic streptococcal empyema. Recent reports certainly justify further trial of this drug. It has been administered both orally and intrapleurally.

The mortality in empyema, provided the established surgical principles previously detailed are followed, is dependent upon the associated complications rather than the empyema itself. The appended list of fatalities confirms this.

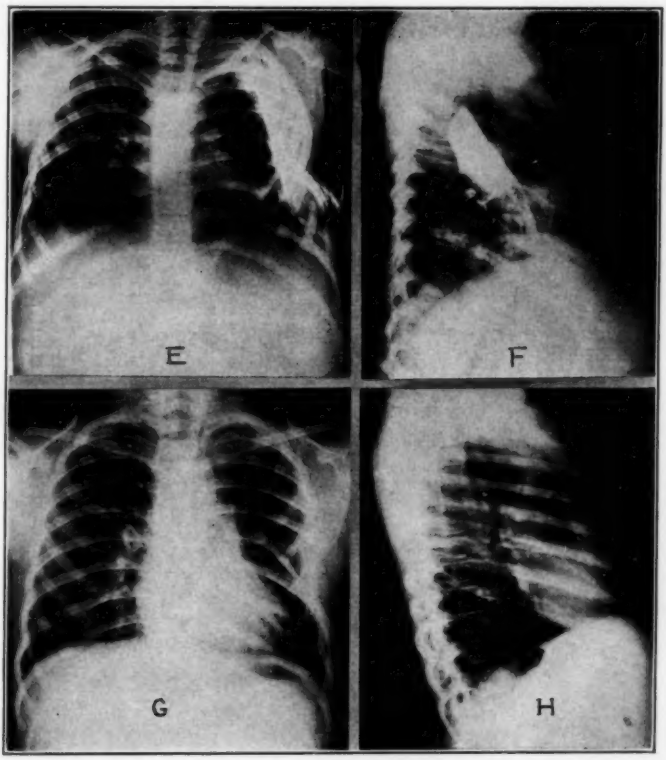

Fig. 4.—*E.* D.E., Oct. 22, 1937. After lipiodol injection into the chest sinus, showing the extent of the cavity remaining one month after rib resection. *F.* Lateral view of previous film. *G.* Feb. 4, 1938. Six months after rib resection. Patient perfectly well. Sinus has completely healed and lungs have reexpanded. *H.* Lateral view of previous film.

EMPYEMA MORTALITY

1. An 8-year-old male, with the left side involved, had one tap and died the ninth day after entry. The patient had a septicemia; there were *Staphylococcus aureus* and streptococcus on culture.

2. A 6-year-old male had empyema involving the left side. *Streptococcus hemolyticus* was found on culture. The patient had septicemia and arthritis; he died on the fifteenth day.

3. A 10-year-old girl with empyema of one year's duration had had numerous tappings and tube drainage. Decortication of the lung was done. The patient died of hemorrhage and shock shortly after operation.

4. A male, 5 years old, developed pneumonia two weeks after tonsillectomy. Rib resection was done for the empyema. Culture showed pneumococcus Type IV and *Streptococcus alpha*. The patient developed bronchopleural fistula and atelectasis. He continued to have drainage and one month after operation was brought in for a muscle filling operation. Autopsy showed bronchopneumonia and bilateral abscesses.

5. A 7-year-old male had hemorrhagic nephritis and pneumonia. Thoracentesis was performed. Fluid showed pneumococcus IV and *Staphylococcus aureus*. The patient had septicemia and developed marked edema. Autopsy showed bronchiectatic abscesses.

SUMMARY

Empyema in children is discussed, with special emphasis on the diagnosis and treatment of this condition.

Sixty cases in children less than 12 years of age are reviewed.

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MENTAL RETARDATION ASSOCIATED WITH CONGENITAL HEART DISEASE

A Study of Twenty-Two Cases

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SINCE congenital anomalies are known to occur in combinations rather than singly, the question of possible association of mental retardation with congenital cardiac defects has been raised. It is a well recognized fact that congenital heart disease is often found in mongolism. Cassel[1] reported eight cases in sixty (13.3 per cent), von Hofe[2] fourteen in 150 (9.3 per cent), and Hill,[3] between 10 and 20 per cent of mongolian idiots as showing congenital heart disease. A persistent defect of the atrial septum is the one most commonly reported. Cook and Millman[4] reported congenital anomalies in two low-grade imbeciles, who died at 3 years of age, and stated: "The coexistence of bicuspid valves and mental deficiency might reasonably be expected, for the occurrence of almost every congenital malformation has been noted in cases of amentia. Nevertheless, we have been unable to find any record of this association unless the case of a hydrocephalic 8-month fetus be taken as a potential imbecile."

The association of physical and mental retardation in school children has been repeatedly studied; but, oddly, tonsils and teeth received most of the attention, and heart conditions, either acquired or congenital, were rarely mentioned. Pope,[5] in a study of "Physical Causes of Slighter Forms of Mental Defect" in children in Leicester and London, found four out of seventy-six and six out of 151, respectively, with cardiac disease, and said, "In a few cases the condition was congenital; in others it was due to rheumatism." Josephine Baker[6] investigated the physical condition of retarded school children whose grade placement was definitely behind the average. She found cardiac disease in 0.5 per cent of all pupils and in 2.3 per cent of the retarded ones. No attempt was made to separate congenital and acquired conditions. Beggs[7] mentioned "defects of the heart and blood" in 5.1 per cent of 272 children studied in an investigation of conditions associated with retardation in elementary school children. Carter[8] found four cardiac lesions in 300 "problem children," and Eisler,[9] in an article concerning the relation of physical disease to behavior problems, mentioned two out of a hundred as showing mitral murmurs. In neither study was there mention of intellectual endowment or differentiation of congenital and acquired

From the Children's Psychiatric Clinic, Harriet Lane Home for Invalid Children, the Johns Hopkins Hospital.

cardiac lesions. Smith[10] felt that cyanosis at birth is a mark of delayed development and a sign of eventual mental retardation but gave no follow-up statistics to bear out this statement. Bostock[11] stated that in mental deficiency "pulmonary stenosis and congenital heart conditions are sometimes serious complications . . . . (and) circulation is poor." He gave no figures on the incidence of these findings. Stevenson,[12] in a study of cardiovascular physiology in mental defectives, spoke of a "less stable circulatory response in lower feebleminded," but made no comment as to the actual anatomic findings in the circulatory system. Weber[13] stated, "Dr. H. Morley Fletcher, however, tells me that congenital heart disease is not rare in imbecile children other than of the mongolian group." Unfortunately no paper of Fletcher's could be found in which he elaborated upon this statement.

In the Harriet Lane Home those working in the cardiac clinic noted that many of the children being followed as having congenital heart lesions had marked difficulty in school and were often placed in special classes. This observation led to the question as to the incidence of mental retardation in patients with congenital cardiac disease. The cardiac and psychiatric clinics of the Harriet Lane Home collaborated in an attempt to answer this question. The cases studied were limited according to age (not more than 14 years) by the admitting rules of the Dispensary, and, in order to have a reasonable expectation of accurate results by the Binet-Simon intelligence tests, no child less than 5 years of age was included. Otherwise no attempt was made to select the cases as to age, race, sex, or degree of cardiac defect. Twenty-two cases were seen, eleven boys and eleven girls ranging from 5 to 14 years of age. Of these, fifteen had been followed in the cardiac clinic, but the diagnosis was well checked in all.

In these cases, patent interventricular septum and patent ductus arteriosus were most common, occurring eight and six times, respectively. Four were diagnosed as patent interauricular septum, two as pulmonary stenosis, one as valvular disease, and in one the pathology was undetermined.

In this group of twenty-two cases none fell in the idiot class but two had I.Q.'s below fifty, thus belonging to the imbecile group; seven fell in the moron group with I.Q.'s of fifty-one to seventy, and eight were in the dull normal group with I.Q.'s of seventy-one to ninety. Only four were within the normal range of ninety-one to 110, and the highest of the group had an I.Q. of 117. There is no relation to the type of lesion, as the two lowest and the one highest in the whole group had been diagnosed as having patent interventricular septum.

This group was compared with a cross section of the Harriet Lane Psychiatric Dispensary patients. One thousand cases within the same age range seen in the Harriet Lane psychiatric clinic were felt to be fairly representative of the general outpatient population. From the

findings in this thousand, one would expect that in twenty-two there would be two with I.Q.'s below fifty, four in the moron group, nine in the dull normal, eight in the normal (91 to 110) and two between 111 and 120. Thus the extremes are approximately the same and the greatest percentage is in the dull normal group in both the cardiac and the general outpatient groups. The difference lies in the number to be found in the moron and the normal groups. This is best shown in Table I. A superimposed graph of the two groups shows this even more clearly (Fig. 1).

It is thus seen that the dull normal range contains the same percentage in each category, but among those with congenital cardiac lesions

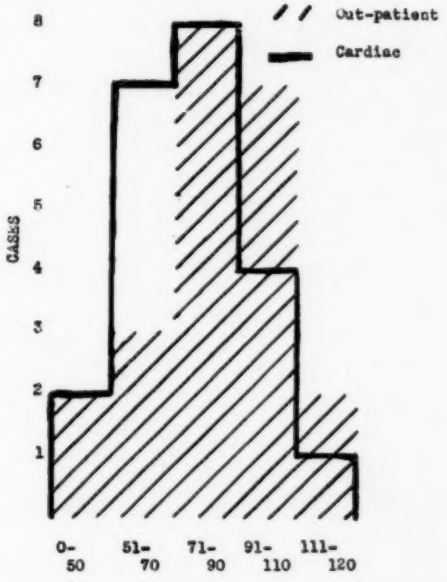

Fig. 1.

the moron group was much larger and the normal group much smaller than is true of a cross section of the outpatient population. In fact, each is almost a mirror image of the other.

TABLE I

I. Q.	CARDIAC		OUTPATIENT	
	NO.	PER CENT	NO.	PER CENT
Under 50	2	9	2	9
51- 70	7	32	3	13.6
71- 90	8	36.3	8	36.3
91-110	4	18.2	7	32
111-120	1	4.5	2	9

Two difficulties arise in attempting to reach any decisions on the basis of this investigation. First, the number studied is entirely too small to allow one to draw definite conclusions; and, second, the difference is not large enough to permit one to discard the suggestion that it is primarily due to a chance selection of cases.

Even so, one feels justified in saying that from a comparison of the findings in twenty-two cases of congenital heart disease with those in a cross section of the psychiatric outpatient population it appears that the intellectual endowment, as measured by the Binet-Simon intelligence tests, tends to be somewhat lower in the group suffering from congenital heart disease.

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A CONTROLLED STUDY OF PERTUSSIS PROPHYLAXIS

A Comparison of Phase I, H. Pertussis Vaccine With Undenatured Bacterial Antigen

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IN MARCH of 1935 an investigation of pertussis prophylaxis was undertaken by a member* of the Pediatric Staff of the University of California Outpatient Department. During a period of three years, observations have been made upon 95 children injected with undenatured bacterial antigen,† 272 children injected with Phase I, *H. pertussis* vaccine,‡ and 256 noninjected children who served as controls for treated groups. This report deals with our method of approach to the problem, a description of each of the groups and the results obtained during a three-year period of observation.

PURPOSE

The purpose of this investigation was critically to evaluate pertussis prophylaxis by careful control of a small group of cases, and to conduct a careful follow up, the nature of which a large group would not permit. We wished to determine: (1) whether injection of pertussis antigen would protect children who were exposed against the disease; (2) whether the course of pertussis was altered favorably in children who were not completely protected; and (3) if protection were conferred, we wished to determine, if possible, the duration of this protection.

PLAN AND METHOD OF STUDY

1. Children included in this study were those referred from the well baby and general pediatrics clinics of the University of California Outpatient Department, who did not have a history of a previous attack of whooping cough or known direct exposure to whooping cough.

2. Immunizing injections were to be given to children who were more than 5 months of age.

From the Department of Pediatrics of the University of California Medical School and the Hooper Foundation for Medical Research. This study was made possible by a grant from the Christine Breon Fund.

*Acknowledgment is hereby made to John J. Miller, Jr., who organized the early part of the investigation.

†Supplied by Eli Lilly and Company. Undenatured bacterial antigen is the protein filtrate obtained after a suspension of the living Phase I, *H. pertussis* cells are mechanically disrupted in a ball mill. Merthiolate 1:100,000 is added to the filtrate as a preservative.

‡Supplied by the Cutter Laboratories. Phase I, *H. pertussis* vaccine is prepared from eight to twenty recently isolated local strains supplied by the author and others. Each culture is tested, not only for hemolysis but also for toxicity and specific agglutinability. Only those cultures which conform to the Phase I grouping of Leslie and Gardner[1] are used. The cultures are grown on Bordet-Gengou human blood media. The vaccine is an unwashed suspension of Phase I organisms, killed with 1:20,000 dilution of merthiolate and diluted with 0.25 per cent phenol saline solution. Two concentrations of vaccine were used in this study, standardized to contain (1) ten billion organisms per cubic centimeter and (2) twenty billion organisms per cubic centimeter.

3. Sibling controls were to be used rather than alternate cases in order to provide the best clinical test of protection conferred by the immunizing injections.

4. An educational program was organized to enlist the cooperation of parents for follow-up visits over a period of years. No charge was made either for the prophylactic injections or the subsequent follow-up visits.

5. Definite appointments for follow-up visits were given at regular intervals of three to four months. Upper respiratory infections developing between appointments were checked by clinic visits to rule out atypical whooping cough. Known exposures occurring between visits were requested to be reported immediately. A careful history was taken of the character (distance between contact and child, in or out of doors, and duration) of each reported exposure. In addition the contact patient was visited for the purpose of taking cough plates and thus determining whether the contact was in the communicable phase of the disease.

As our study progressed, we found that we were not able to attain the ideal of sibling controls for all of the treated children. A number of the children referred to us were either an only child or the only sibling of the family who did not have a previous attack of pertussis. We expected to follow our groups for a period of five years. The possibility that chance exposure might not occur before additional members were added to the family group seemed to justify our giving the only child member of the family prophylactic injections and the use of the subsequent members as sibling controls. We have also used as controls children whose parents objected to prophylactic measures.

CRITERIA FOR EXPOSURE

1. In the group where siblings were available, exposure comprises contact with the child suffering with pertussis (proved bacteriologically).

2. For children where siblings were not available, exposure comprises:

a. Known close contact (at play, parties, meals, etc., during which time frequent coughing occurred) with a child who has whooping cough and who has been proved by cough plates to be in the communicable phase of the disease.

b. If the exposure is reported to have taken place out of San Francisco, over week ends or other visits, cough plate follow-up on the contact is not possible. When this occurs, our criteria for direct exposure are based upon the history of typical whooping cough developing in the susceptible contact patient who was exposed at the same time, in the same manner, and for the same duration as the child reported in our group.

c. The development of clinical pertussis (proved bacteriologically) without a history of known exposure to pertussis.

By application of these criteria, we were able to determine whether direct exposure occurred and to eliminate the instances of indirect and improbable exposure. In as much as pertussis cases are seldom isolated, daily contact with children in the communicable phase of the disease occurs with considerable frequency. While, perhaps, this is not equal to exposure by sibling, nevertheless it serves as a good control for the injected children who do not have sibling controls and who were exposed in this manner. These criteria for exposure to pertussis are severe tests and it is possible that more exposures occurred than are reported.

DESCRIPTION OF EACH GROUP AND THE RESULTS OBTAINED

I. *Undenatured Bacterial Antigen* (Krueger).—Undenatured bacterial antigen was used as a prophylactic against pertussis from March 1 to Dec. 31, 1935. During this period, ninety-five children were injected with this antigen. A total dose of 10 c.c. for each child was divided and given at each of three visits at intervals of one week. A small amount was injected intracutaneously, and the remainder was given subcutaneously. The age grouping of the ninety-five children was as follows:

Less than 1 year	35 (36.7 per cent)
1 to 2 years	17 (17.8 per cent)
2 to 3 years	10 (10.5 per cent)
3 to 5 years	15 (15.9 per cent)
More than 5 years	18 (18.9 per cent)
Total	95

Sibling controls are available for seventy-seven of the ninety-five children, and eighteen do not have sibling controls.

Results.—The number of exposures, cases, and escapes which occurred in each of the age groups is shown in Table I. A summary of the exposures, cases, and escapes which occurred in the group of seventy-seven sibling controlled children and in the group of eighteen without sibling control is shown in Table II.

TABLE I

NUMBER OF EXPOSURES, CASES, AND ESCAPES WHICH OCCURRED IN EACH AGE GROUP*

AGE	TOTAL NUMBER	NUMBER EXPOSED	PERTUSSIS CASES	ESCAPES
Less than 1 year	35	11	9	2
1 to 2 years	17	8	7	1
2 to 3 years	10	5	3	2
3 to 5 years	15	6	5	1
More than 5 years	18	4	4	0
Totals	95	34	28	6

*Ninety-five children injected with undenatured bacterial antigen.

In the total of 95 children there were 34 who were directly exposed to pertussis, and 28, or 82.3 per cent, of these exposed children developed whooping cough. One child had two attacks (both proved bacterio-

TABLE II

SUMMARY OF EXPOSURES, CASES, AND ESCAPES WHICH OCCURRED IN THE SIBLING CONTROLLED AND THE NONSIBLING CONTROLLED PATIENTS*

	NUMBER OF CHILDREN	NUMBER OF EXPOSURES	PERTUSSIS CASES	ESCAPES
Children controlled with siblings	77	23	19 (82.6%)	4 (17.4%)
Children who were not controlled with siblings	18	11	9 (81.8%)	2 (18.2%)
Totals	95	34	28 (82.3%)	6 (17.6%)

*Ninety-five children injected with undenatured bacterial antigen.

logically) which occurred thirteen months apart. The second attack was very mild. The 28 attacks of whooping cough (excluding the second attack which occurred in one child) are classified roughly as follows:

ATTACK INTENSITY	NUMBER OF PATIENTS
Severe	6
Moderately severe	11
Moderate	8
Mild	3

In the group of 77 children controlled with siblings there were 23 who were exposed to pertussis and 19, or 82.6 per cent, of these developed the disease. In the group of 18 children who were not controlled with siblings 11 were exposed and 9 (81.8 per cent) of these developed pertussis. There were only 6 (17.6 per cent) of all the exposed children who escaped. These data do not support the view that undenatured bacterial antigen confers protection against pertussis.

II. *Phase I, H. Pertussis Vaccine.*—Between September, 1935* and May, 1938, Phase I, *H. pertussis* vaccine† was used as the prophylactic agent against pertussis. During this period 272 children were injected with this antigen. Except for 10 children who did not return after the first injection (ten billion organisms) all of the 272 children received a total dose of eighty billion organisms. No severe reactions have been encountered. To minimize minor complaints (fussiness of twelve hours' duration) we prescribe two doses of acetylsalicylic acid of one grain per year of age of child, to be given three hours apart on the day of injection. The age grouping of the 272 children was as follows:

Less than 1 year	138 (51.1 per cent)
1 to 2 years	69 (25.3 per cent)
2 to 3 years	29 (10.6 per cent)
3 to 5 years	26 (9.5 per cent)
More than 5 years	10 (3.6 per cent)
Total	272

*During a four-month period (September to December 31, 1935) both undenatured bacterial antigen and Phase I, *H. pertussis* vaccine were used. The undenatured bacterial antigen was discontinued entirely after Dec. 31, 1935, and since that time Phase I, vaccine has been the only prophylactic used.

†For a period of one year we used pertussis vaccine standardized to contain ten billion organisms. Since November, 1936, pertussis vaccine standardized to contain twenty billion organisms per cubic centimeter has been used routinely. This concentration permitted our giving the total amount at one site at each visit, as follows: First injection 1 c.c., total twenty billion organisms, second and third injections each 1.5 c.c. Total each thirty billion organisms. Injections are given at weekly intervals.

Sibling controls are available for 162 of the 272 children, and 110 do not have sibling controls.

Results.—The number of exposures, cases, and escapes which occurred in the different age groups is shown in Table III. A summary of the exposures and escapes which occurred in the group of 162 children controlled with siblings and the 110 children without sibling controls is shown in Table IV.

TABLE III

NUMBER OF EXPOSURES, CASES, AND ESCAPES WHICH OCCURRED IN EACH AGE GROUP*

AGE	NUMBER OF CHILDREN	NUMBER EXPOSED	PERTUSSIS CASES	ESCAPES
Less than 1 year	138	18	5†	13
1 to 2 years	69	10	1†	9
2 to 3 years	29	5	1	4
3 to 5 years	26	8	0	8
More than 5 years	10	1	0	1
Totals	272	42	7	35

*Group of 272 children injected with Phase I, *H. pertussis* vaccine.
†One child in each of these age groups had dose of ten billion organisms.

TABLE IV

NUMBER OF EXPOSURES, CASES, AND ESCAPES WHICH OCCURRED IN THE SIBLING CONTROLLED GROUP AND THE GROUP WITHOUT SIBLINGS*

	NUMBER OF CHILDREN	NUMBER OF EXPOSURES	PERTUSSIS CASES	ESCAPES
Children who were controlled with siblings	162	28	5 (17.8%)	23 (82.2%)
Children who were not controlled with siblings	110	14	2 (14.2%)	12 (85.8%)
Totals	272	42	7 (16.6%)	35 (83.4%)

*Group of 272 children injected with Phase I, *H. pertussis* vaccine.

In the total group of 272 children injected with pertussis vaccine, 42 were exposed to pertussis, and 7 (or 16.6 per cent) of the exposed children developed *H. pertussis* infection. The following observations of the 7 cases of pertussis are of interest:

1. Four months after a total dose of eighty billion organisms one of the patients developed a nonparoxysmal cough of three days' duration, and it may be assumed that he had an abortive attack of pertussis, even though clinical and bacteriologic diagnosis was lacking. A week after this "mild cold" cleared up, the 5-week-old sister, who had no other possible source of exposure to pertussis, developed a cough and positive cough plates were obtained. The infant had a severe attack of pertussis, and although the older brother was in daily contact with his sister throughout the entire course of the disease, he developed no further symptoms.

2. One of the 7 patients was subjected to two intimate exposures. The first exposure occurred four months after vaccine injection (dose eighty billion). At this time the patient was intimately exposed daily for a ten-day period to a foster child who was in the coryzal and early paroxysmal stage of whooping cough. No symptoms developed. Two years later (two years and four months after vaccine injection) this patient was again intimately exposed in another foster home, and after this exposure he developed a moderate attack of pertussis (proved bacteriologically).

3. One of the 7 patients subjected to familial exposure six months after injection of pertussis vaccine (dose eighty billion) developed a moderate attack of pertussis.

4. Another of the patients, an only child, was exposed outside of the family, twenty-seven months after injection of pertussis vaccine (dose eighty billion), and this child developed a moderately severe attack.

5. The fifth patient, after being subjected to repeated nonfamilial exposure, developed a mild attack of pertussis about two and one-half months after injection (paroxysmal cough, two weeks' duration; no whoop, no vomiting).

6. Two of the patients received a total dose of only ten billion organisms. Approximately eighteen months after injection of vaccine both of these children developed typical whooping cough. The attacks were moderate.

Thus it will be noted that of the 7 cases of pertussis which occurred in this group, 1 was moderately severe, 4 were moderate, and 2 were mild (1 having had cough for only three days).

In contrast to the one child who showed evidence of protection four months after immunizing injection and no protection twenty-eight months after immunizing injections, we have noted that 6 of the 35 exposed children who escaped have been subjected to direct exposure at least twice. Two of these 6 escapes were directly exposed three times. These latter exposures occurred thirty months after the immunizing injections. The possibility that these latter exposures may also act as immunizing silent infections should not be overlooked.

In the group of 162 children, injected with pertussis vaccine, who were controlled with siblings, there were 28 exposed, and 5 (17.8 per cent) of these developed attacks. In the group of 110 who were not controlled with siblings, 14 were exposed and 2 (or 14.2 per cent) developed attacks. These communicability rates are in marked contrast to the communicability rate (82.5 per cent) of the sibling controlled undenatured bacterial antigen group and (81.8 per cent) of the nonsibling controlled undenatured bacterial antigen group. In the group of 42 exposed children who were injected with pertussis vaccine, there were 35 (or 83.3 per cent) who escaped. This protection rate is also in great contrast to the same rate (17.6 per cent) for the undenatured bacterial antigen group.

III. *Control Group.*—The control group, under observation since March, 1935, comprises 256 nonimmunized children who serve as controls for both groups of injected children. The age grouping of the 256 children is as follows:

Less than 1 year	67 (26.1 per cent)
1 to 2 years	24 (9.3 per cent)
2 to 3 years	22 (8.6 per cent)
3 to 5 years	51 (19.9 per cent)
More than 5 years	92 (35.9 per cent)
Total	256

Of the 256 controls, 207 are siblings,* and 49 are nonsiblings.

*In a number of instances these siblings serve as control for both vaccine and undenatured bacterial antigen. Between September and December, 1935 (the four-month period during which both antigens were used) in families of three or more children, one child was injected with undenatured bacterial antigen, one with pertussis vaccine, and the third or remaining children served as controls for both injected children.

Results.—The number of exposures, cases, and escapes which occurred in the different age groups is shown in Table V. A summary of the exposures, cases, and escapes which occurred in the group of 207 siblings and the group of 49 nonsiblings is shown in Table VI.

TABLE V

THE NUMBER OF EXPOSURES, CASES, AND ESCAPES WHICH OCCURRED IN VARIOUS AGE GROUPS OF THE 256 CHILDREN WHO SERVED AS CONTROLS FOR THE INJECTED CHILDREN

AGE	NUMBER OF CHILDREN	NUMBER EXPOSED	CASES	ESCAPES
Less than 1 year	67	11	10	1
1 to 2 years	24	12	11	1
2 to 3 years	22	10	8	2
3 to 5 years	51	18	17	1
More than 5 years	92	20	16	4
Totals	256	71	62	9

TABLE VI

THE NUMBER OF EXPOSURES, CASES, AND ESCAPES WHICH OCCURRED IN THE CONTROL GROUP OF SIBLINGS AND NONSIBLINGS

	NUMBER IN GROUP	NUMBER EXPOSED	CASES	ESCAPES
Siblings	207	47	41 (87.2%)	6 (12.8%)
Nonsiblings	49	24	21 (87.5%)	3 (12.0%)
Totals	256	71	62 (87.2%)	9 (12.6%)

In the total group of 256 children, 71 were exposed to pertussis and 62 (or 87.2 per cent) developed attacks. One child in this group (sibling control for undenatured bacterial antigen) had two attacks (proved with cough plates) approximately one year apart. Both were mild. The 62 attacks of whooping cough (excluding the second attack which occurred in one child) are classified roughly as follows:

ATTACK INTENSITY	NUMBER OF PATIENTS
Severe	10
Moderately severe	22
Moderate	24
Mild	6
Total	62

In the group of 207 siblings, there were 47 exposures, and 41 (or 87.2 per cent) developed pertussis. In the group of 49 nonsiblings, 24 children were exposed, and 21 (or 87.5 per cent) developed pertussis. Only 9 (or 12.6 per cent) of the 71 exposed children escaped.

When siblings are used as controls, rather than alternate cases, it is not possible to have the same number in each age group represented. In our series, 65 per cent of the children injected with undenatured bacterial antigen, 87 per cent of the children injected with pertussis vaccine, and only 44 per cent of the control children were less than 3 years of age. Thus it would seem that the possibility of exposure was greatest in the control group of children, since a large number were

in the preschool and school age groups. But the fact that older children may be less susceptible should also be considered, and this factor may have favored our control group. A high percentage of the injected children were in the more susceptible age groups and consequently the possibility of developing pertussis after exposure was greater in these children than in the control group.

For comparison of the findings in the three groups, the results of each are summarized in Table VII.

TABLE VII
SUMMARY OF RESULTS OF OBSERVATION OF PERTUSSIS PROPHYLAXIS FOR A THREE-YEAR PERIOD*

GROUP	TOTAL NUMBER	EXPOSURES	CASES	RATE OF COMMUNICABILITY†	ESCAPES	RATE OF PROTECTION†	RATE OF ATTACK†	ESTIMATE OF CLINICAL COURSE IN CASES	
1	95	34	28‡	82.3%	6	17.6%	29.4%	Severe	6
								Mod. severe	11
								Moderate	8
								Mild	3
2	272	42	7§	16.6%	35	83.4%	2.5%	Severe	0
								Mod. severe	1
								Moderate	4
								Mild	2
3	256	71	62‡	87.2%	9	12.6%	24.2%	Severe	10
								Mod. severe	22
								Moderate	24
								Mild	6

*Three groups were observed: (1) children injected with undenatured bacterial antigen; (2) children injected with Phase I, *H. pertussis* vaccine; (3) noninjected control children.

†Rates: Communicability refers to the percentage of exposed children who developed pertussis. Protection refers to the percentage of exposed children who escaped. Attack refers to the percentage of the total number (both exposed and nonexposed) who developed pertussis.

‡One child had two attacks of pertussis.

§Two of these children received only one injection of ten billion organisms.

In comparing the findings in each of the groups (Table VII), it will be noted that there is a difference of only 4.9 per cent between the communicability rate of the group injected with undenatured bacterial antigen and the control group. On the other hand, a comparison of the group injected with pertussis vaccine and the control group shows a difference of 70.6 per cent in the communicability rate. Noteworthy difference is also observed in connection with the attack rate. In the case of the undenatured bacterial antigen group and the control group there is a difference of 5.4 per cent. But between the pertussis vaccine group and the control group there is again the more striking difference of 21.7 per cent. These differences are shown graphically in Fig. 1.

In the short period of time that our groups have been under observation, we have encountered two children who had second attacks occurring approximately one year apart. During the observation of the 97 cases of pertussis which occurred in children of the three groups studied, we have encountered, in addition, 6 cases, in adults (parents) who had histories of having had whooping cough during childhood.

These 6 attacks were mild (paroxysmal coughs for short duration without whoops) and undoubtedly would have escaped notice if cough plates had not been taken.

COMPARISON OF RESULTS WITH CONTROLLED OBSERVATIONS OF PERTUSSIS PROPHYLAXIS REPORTED IN LITERATURE

Recognition and credit must go to Sauer, not only for having been among the first to attempt immunization against pertussis, but also for the stimulus his work has provided in encouraging other workers to

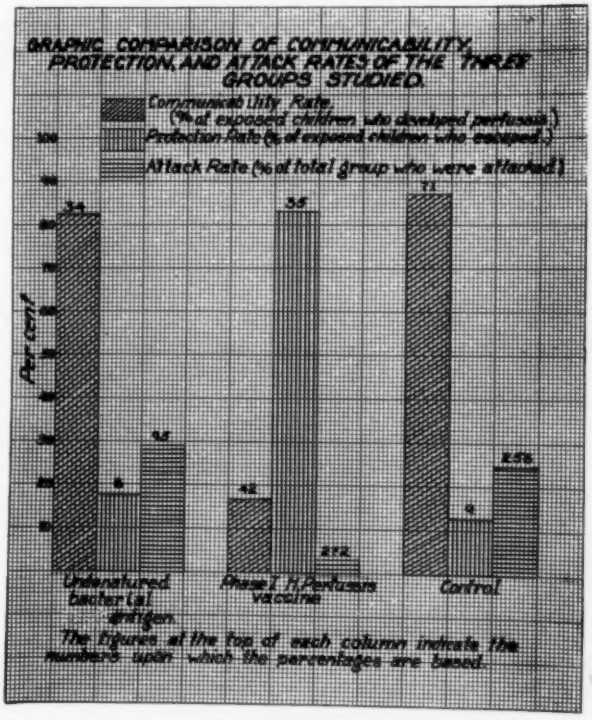
GRAPHIC COMPARISON OF COMMUNICABILITY, PROTECTION, AND ATTACK RATES OF THE THREE GROUPS STUDIED.
Communicability Rate (% of exposed children who developed pertussis)
Protection Rate (% of exposed children who escaped)
Attack Rate (% of total group who were attacked)
Per cent
34
6
42
42
55
2?2
71
4
25?
Undenatured bacterial antigen
Phase I H. Pertussis vaccine
Control
The figures at the top of each column indicate the numbers upon which the percentages are based.

Fig. 1.

pursue investigation of this subject. During the past ten years a number of observations on prophylaxis with Phase I, *H. pertussis* vaccine have been reported in the literature. A review of this subject is not necessary since it has been treated adequately by others.[2] It is unfortunate that a comparable number of controls have not been included in all these studies. Not only the dosage of vaccine given, but also the preparation of vaccine used, has varied with the investigator in a number of instances. The conditions under which these observations have been made also differ. Some observations have been made during

epidemics when the intensity of infective dosage was great. The population, urban in contrast with rural, and the age groups have also varied. The use of the attack rate as an index without qualification is likely to be very misleading. The response to exposure of the infecting agent (the communicability rate), is likely to be a more constant factor and recommends itself as a more reliable index for comparison.

A summary of the controlled observations on pertussis prophylaxis reported in the literature is shown in Tables VIII and IX. The treated groups are summarized in Table VIII and the control series of each investigation in Table IX.

Madsen's[3] observations of a large number of children subjected to epidemic exposure in the Faroe Islands showed that while a dosage of twenty-two billion killed organisms was inadequate for complete protection, in all the cases, the mortality and severity of attack in the injected group were considerably reduced as compared with the control group. In our series the dosage used was considerably greater than that used by Madsen. Two of the exposed children who developed attacks had received small dosage.

Our results with Phase I, *H. pertussis* vaccine compare favorably with those of Kendrick,[4, 5] whose controlled study comprises observations of a group of 4,575 children during a five-year period. The dosage of vaccine used by Kendrick was similar to the dosage used in our series. The preparation of vaccine used has varied slightly. The communicability rate in our vaccine injected series was 16.6 per cent compared with 15.8 per cent reported by Kendrick. In the control series our communicability rate of 87.2 per cent is comparable with 77.7 per cent of Kendrick's control group, considering the difference in the size of the respective groups.

Our results are not reconcilable with the observations of Doull, Shibley, and McClelland[6] who reported attack rates only (12.7 per cent in the treated group and 14.1 per cent in the control group). However, these investigators report: "It is the impression of the physicians who have seen representative cases of both series that attacks among the inoculated tend to be milder."

The small but well-controlled observation of Siegel and Goldberger[7] and of Kramer[8] is of great interest and value. In contrast with most observations on pertussis prophylaxis, these investigators had the rare opportunity to observe three groups of children [those with (1) no previous attack and no vaccination, (2) definite previous attacks, and (3) pertussis vaccine injections], all of whom were intimately exposed during an epidemic which occurred in institutions. The intensity of the infective agent may be considered great in all of the exposed children. It is unfortunate that bacteriologic examinations were not made in either of these studies so that the diagnosis would have been clearly established. The incidence of whooping cough in the three exposed

TABLE VIII

SUMMARY OF RESULTS OF CONTROLLED OBSERVATIONS IN PERTUSSIS PROPHYLAXIS REPORTED IN THE LITERATURE

TREATED GROUP

AUTHOR	DOSAGE BILLION	NUMBER CHILDREN	EXPOSURES	CASES	COMMUNICABILITY RATE	ESCAPES	PROTECTION RATE	AUTHOR'S COMMENT ON CLINICAL COURSE
Madsen 1929 Epidemic	22	1832		1347		458	25.0%	Mild 1336 Moderate 29 Severe 8 Fatal 1
Kendrick 1936	75	975	95	13	13.6%	82	86.3%	9 cases (or 62.2%) were light or very light
Kendrick* 1937	75	2205	284	45	15.8%	239	84.2%	Very light 17 Light 15 Moderate 12 Severe 1 Fatal 0
Doull, Shibley, McClelland	80	483		61				"Attack rate—12.5%. Attacks in inoculated group tend to be milder."
Siegel and Goldberger	80	101	17	9	53.0%	8	47.0%	"Average duration of whoop is 21 days" Moderate severe 1 Mild 2 Very mild 4
Kramer	80	50	9	8	88.0%	0	11.0%	Mild 6 Av. 3 weeks Very light 2 1 lasted 1 week 1 lasted 1 day

*Personal communication.

TABLE IX

CONTROL GROUP

AUTHOR	HIST. PREV. ATTACK	NUMBER CHILDREN	NUMBER EXPOSED	CASES	COMMUNICABILITY RATE	ESCAPES	PROTECTION RATE	AUTHOR'S COMMENT ON CLINICAL COURSE
Madsen 1929 Epidemic		446		438		8	2.2%	Mild 225 Moderate 170 Severe 35 Fatal 8
Kendrick 1936	Negative	950	128	98	75.5%	30	23.4%	19 cases (or 19.3%) were light or very light
Kendrick* 1937	Negative	2370	354	275	77.7%	79	23.3%	Very light 11 Light 54 Moderate 166 Severe 44 Fatal 0
Doull, Shibley, McClelland	Negative	496		71				Attack rate 14.1% 1 fatal case
Siegel and Goldberger	Negative	82	19	11	58.0%	8	40.0%	Average duration of whoop is 32½ days Fatal 1 Moderate severe 5 Moderate 4 Mild 1
	Positive	16	16	5	31.0%	11	67.0%	"Disease was mild in most instances"
	Questionable	12	12	6	50.0%	6	50.0%	
Kramer	Negative	50	12	12	100.0%	0	0.0%	Duration of paroxysmal cough: 10 cases 7 weeks 2 cases 5 weeks
	Positive	8	8	8	100.0%	0	0.0%	Duration of cough 6 cases 3 weeks 2 cases 1 week

*Personal communication.

groups observed by Siegel and Goldberger varied between 31.0 per cent and 58.0 per cent, while Kramer reported a variation of 88 per cent and 100 per cent in the three groups.

It is very significant, however, that these investigators report that the attacks in the vaccinated children are very similar to the attacks in children with a positive history of whooping cough. The mild course of the disease in these groups was in marked contrast with the disease in the control group. Their observations would seem to indicate that vaccination conferred as much protection as that derived from a previous attack.

We have not had an opportunity to observe our groups under similar conditions. In the short period of time that our series has been under observation, however, we have noted second attacks in two children and six adults, all of which were proved bacteriologically. All of these attacks were mild.

COMMENT

Our observation, and the controlled observations reported in the literature favor the use of large dosage (eighty billion organisms) of Phase I, *H. pertussis* vaccine as a prophylactic against pertussis. It would appear that the magnitude of protection conferred by injection of vaccine is similar to that conferred by clinical whooping cough. This seems to be apparent from the incidence of complete protection observed in the vaccinated children and those who have had whooping cough. It is further supported by the observation that not only the children who have had whooping cough, but also the vaccinated children who develop the disease usually have mild attacks.

Our group has not been observed over a sufficient interval to permit the determination of the duration of protection. One case is presented which furnished evidence of complete protection four months after immunization and lack of this protection twenty-seven months after immunization. A considerably longer period of observation must be allowed before final conclusions can be drawn from our series.

There is great need for fundamental investigation of the nature of immunity in pertussis.

The routine use of cough plates to establish the diagnosis in atypical and abortive cases will undoubtedly reveal the fact that second attacks of pertussis are not as much of a rarity as they have been considered.

A successful program for pertussis prophylaxis cannot be achieved until more data are available on the following:

1. The nature of the mechanism of immunity in pertussis.
2. The preparation of an adequate pertussis antigen.
3. The standardization of such an antigen.
4. The use of standardized antigen on a large controlled series intimately followed for a period of years.

5. The use of cough plates as a means of determining exposure to living *H. pertussis* organisms.

SUMMARY

1. An outline of our investigation for the study of pertussis prophylaxis is given.

2. During a three-year period observations were made upon: (1) 95 children injected with undenatured bacterial antigen; (2) 272 children injected with Phase I, *H. pertussis* vaccine; (3) 256 control children.

3. In the group of 95 children injected with undenatured bacterial antigen, there were 34 children who were exposed and 28 (or 82.3 per cent) who developed pertussis. Six (or 17.6 per cent) of the exposed children escaped attack. The attack rate in the total of 95 children was 29.4 per cent.

4. Of the 272 children injected with Phase I, *H. pertussis* vaccine, there were 42 who were exposed to pertussis. Of these, 7 (or 16.6 per cent) developed *H. pertussis* infections. Thirty-five (or 83.4 per cent) of the 42 exposed children escaped. The attack rate in the total group of 272 children was 2.5 per cent.

5. Of the 256 control children, there were 71 exposed to pertussis, and 62 (or 87.2 per cent) of these developed attacks. Nine (or 12.6 per cent) of the exposed children escaped. The attack rate in the total group of 256 children was 24.2 per cent.

6. A comparison of our observations is made with that of other controlled studies reported in the literature.

7. There is included a discussion of the evidence that protection conferred by active immunization with pertussis vaccine is similar to that of a previous attack of the disease.

CONCLUSION

In a controlled study of pertussis prophylaxis, the demonstrable immunity conferred by the use of undenatured bacterial antigen was found to be negligible. In our Phase I, *H. pertussis* vaccine series 83.4 per cent of the exposed children did not develop the disease. Our group has not been observed over a sufficiently long period to determine conclusively the duration of this protection.

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THE NEUROLOGICAL COMPLICATIONS OF WHOOPING COUGH

A Review of the Literature With the Reports of Two Cases of Pertussis Encephalitis

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THE importance of whooping cough as a cause of childhood mortality and the frequent occurrence of serious sequelae from that disease are generally recognized. However, the high incidence of pulmonary complications so greatly overshadows those of the nervous system that these latter have received but scant attention in textbooks dealing with diseases of children. The medical literature, too, contains relatively few articles on the neurological complications of pertussis, with most of these in the foreign literature. In view of the foregoing, it seems desirable that all cases of whooping cough complicated by disorders of the central nervous system should be reported, and timely that a review of the literature on the subject should appear.

REVIEW OF THE LITERATURE

The occurrence of neurological complications in pertussis was noted as early as 1842 by Barrier,[1] 1844 by Rilliet and Barthez,[2] and 1866 by Trousseau.[3] West,[4] in 1899, and Luce[5] in the same year reported the first autopsies on victims of this condition. Both demonstrated minute hemorrhages, edema, and cellular degeneration of the brain in their cases. Schreiber,[6] in 1899, reviewed the reports of thirty-eight cases with eleven deaths and ten autopsies. He reported minute hemorrhages in various parts of the brain as the chief finding but felt these insufficient to account for the outcome and clinical course; he suggested that a microscopic examination might have demonstrated a more diffuse cellular change of hemorrhagic or encephalitic nature. Hockinjos,[7] in 1900, studied the records of forty-two cases diagnosed as having intracranial hemorrhage during whooping cough. A few of the cases included autopsy reports with the chief finding minute hemorrhages in the brain. He, like Schreiber, felt these insufficient to explain the course of the disease. Valentine,[8] in 1902, reviewed the records of eighty-three patients with severe attacks of whooping cough. Of these, sixty-four had convulsions, and of these, fourteen died, twenty-two developed spastic paralyses, and twenty-eight showed some other residual neurological disturbances.

Neurath,[9] in 1904, demonstrated early meningeal changes in cases of whooping cough with convulsions and concluded that there was a diffuse inflammation throughout the brain, probably of toxic origin. Other writers have been unable to agree with the meningeal findings.

Rhein,[10] in 1905, reported a case with multiple minute hemorrhages of the brain, Hada[11] in writing of the "meningeal complications of whooping cough" described "an acute encephalitic change in parts of the brain adjacent to a profuse exudate in the sulci." Hada called attention to the similarity in these cases and cases of encephalitis complicating influenza. Canelli,[12] in 1919, after examining the

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brains of two infants dying with convulsions during the course of pertussis, advanced the theory that the minute hemorrhages which he demonstrated had occurred either as a result of the action of carbon dioxide on the vessels during the asphyxia of a paroxysm of coughing or because of the increased intraventricular pressure resulting from the coughing attack. Reiche,[13] in 1920, in writing of pertussis, expressed the opinion that the occurrence of convulsions was a very unfavorable sign.

Bluhdorn,[14] in 1920, reported low blood calcium as a cause of convulsions occurring during whooping cough. Similar observations have been made by Powers,[15] in 1925, and Trambusti and Sertori,[16] in 1931.

Husler and Spatz,[17] in 1924, demonstrated irreversible degenerative changes of the cortex, dentate nucleus, and corpus striatum without hemorrhage in two patients dying of whooping cough complicated by convulsions. They described a typical regressive change in the nerve cells of the cortex with loss of staining properties and all structure of the cell except the nucleus. The work of these two men aroused considerable interest as it provided the first definite evidence against a hemorrhagic basis for the neurological complications of pertussis and suggested an encephalitic foundation for their occurrence.

Neuberger,[18] in 1925, described lesions like those of Husler and Spatz[17] in two cases, but thought the changes due to ischemic necrosis resulting from air emboli secondary to a ruptured alveolus. Jochims,[19] in 1928, confirmed the Husler and Spatz[17] findings in a case at autopsy and suggested the term "whooping cough encephalopathy." Berardi,[20] in 1927, reported two cases of pertussis with cerebral complications, in both of which complete recovery occurred, and termed them both encephalitis. Blasi,[21] in the same year, also reported a case of pertussis encephalitis with complete recovery. Ford,[22] in 1928, reported the autopsy findings in two cases. He described flattened convolusions, disappearance of the sulci, edema, universal atrophy of the cortical cells, a proliferation of neuroglia, and slight dilatation of the ventricles. Singer,[23] in the same year, reported the findings of a diffuse, hemorrhagic encephalitis in six cases of pertussis with cerebral complications. Singer was so impressed by the hemorrhagic nature of the condition that he felt pertussis encephalitis could be differentiated from the epidemic variety by the marked tendency to microscopic hemorrhages in the former.

Litvak,[24] in 1928, reviewed the reports of seventeen cases of pertussis in which visual disturbances occurred. He attributed these to hemorrhages into the posterior limb of the internal capsule, encephalitis, multiple hemorrhages of the retina, and toxicity. Lazarus and Levine,[25] in 1934, reported a case of blindness after pertussis and reviewed the findings in seventeen cases collected from the literature. They reported that in more than 50 per cent of the eighteen cases, there were present other cerebral manifestations of underlying pathology. They felt that cerebral edema or acute hemorrhagic encephalitis accounts for ocular changes in the majority of instances.

Askin and Zimmerman,[26] in 1929, reported the autopsy findings in a case of pertussis encephalitis in a 4-month-old infant. The autopsy, which was performed three hours after death, showed no atrophy and no hemorrhage over the surface of the brain, although there was a small circumscribed hemorrhage at the base of the brain. Petechial hemorrhages were strikingly absent. Sections from the cerebral hemispheres showed focal collections of small, deep-staining mononuclear cells with occasional large, pale, mononuclear cells with vesicular nuclei and abundant cytoplasm. Sears,[27] in 1929, reported three cases, two with meningeal syndromes and one with right hemiplegia, with complete recovery in all. Sakanchi,[28] in 1928, described changes in the brain similar to those described by Husler and Spatz.[17]

Yamaoka,[29] in 1929, studied histologically the brains of three individuals dying of pertussis, in only two of whom had convulsions occurred. In none of the cases

was hemorrhage or inflammation demonstrated. In the patient dying without convulsions, no significant changes in the brain were found, but in the other two there were changes which he considered elective and characteristic. In one patient, in which only mild convulsions had occurred, only the cerebellum was involved, while in the other, which had been attended with severe convulsions, Ammon's horn, Sommer's sector, and the end leaf, excepting the thick zone, in addition to the Purkinje cells of the cerebellum, the anterior half of the palladium, and the anterior nucleus of the thalamus were altered. The changes consisted of ischemia or homogenization of vasogenic origin with the accompanying gliosis and capillary proliferation. Since the areas involved are the areas deficiently provided with vascular supply, and as the vessels in these areas seemed normal, Yamaoka offered the explanation that a functional disturbance of the circulation, perhaps an angiospasm, was responsible. Since the degree of change in the brain ran parallel with the severity of the convulsions in his patients, he felt that angiospasm of the cerebral vessels bore a close relationship to the occurrence of convulsions in whooping cough.

Mikulowski,[30] in 1930, advanced the opinion that the blood in pertussis contains a toxin capable of affecting the tissues of the central system and the endothelial lining of the vessels thereof.

Eley,[31] in 1930, reviewed the literature on the neurological complications of whooping cough, and reported his findings in four cases with neurological sequelae presumably attributable to pertussis. His report is particularly interesting, because in three of his cases he made encephalograms. One showed calcified areas in the brain which he attributed to old areas of hemorrhage, and the other two showed cortical atrophy with markedly dilated ventricles. His report clearly shows that neurological symptoms occurring during whooping cough may result later in mental retardation, spastic paralysis, visual disturbances, etc.

Hiller and Grinker,[32] in 1930, made a comprehensive study of the cerebral complications of whooping cough, and attempted to explain the occurrence of these complications by applying the theory of "stasis and prestasis." Richer,[33] in 1919, demonstrated that a slight stimulation of the vasomotor nerves results in a dilatation of the blood vessels with acceleration of the blood stream. A stronger stimulation leads to vasoconstriction followed by a dilatation of the capillaries, and when this is accompanied by a slowing of the circulation, prestasis with petechiae usually occurs. Such a state frequently develops into a stasis, and if this develops rapidly agglutination of the blood cells may occur. A stasis is not accompanied by the transudation of serum, whereas in prestasis there is likely to be transudation with diapedesis of erythrocytes also taking place. A combination of the necrotic effect of stasis, as in a softening, with the resulting prestasis of the surrounding tissue leads to a red infarction. When prestasis is not followed by stasis there results an incomplete necrosis with hyperplasia of the mesodermal and glial elements in the nervous tissues. Hiller[34] and Grinker,[35] in 1924, and Meyer,[36] in 1925, demonstrated characteristic areas of softening in the brain caused by the action of carbon monoxide poisoning on the cerebral vessels on the basis of prestasis and stasis, showing that functional disturbances of the blood supply may lead to lesions of nervous tissue of a severity as great as organic circulatory disturbances.

Neuberger,[37] in 1926, and Spielmeyer,[38] in 1928, demonstrated that the lesions caused by stasis and prestasis in the brain were identical with those of organic vascular occlusions, especially those lesions in the gray matter. According to Hiller and Grinker,[32] "there is apparently a gradual transition from a repairable disturbance of brain function on a functional circulatory basis (the explanation of certain transient nervous symptoms) to permanent defects." They made a thorough study of the brain of a 3-year-old child dying with convulsions and paralysis

of the left side that developed during pertussis. They found cortical softenings of the right side with distention of the cortical vessels. Over the abnormal cortex there were large numbers of proliferative macrophages with pyknotic nuclei undergoing regressive changes. Some of the cells contained small amounts of fat and were most numerous about the vessels. There were three degrees of severity to the pathologic process: the first stage consisting of astrocytic proliferation with degeneration of the ganglion cells and an increased number of microglia cells filled with fat; the second stage was one of incomplete softening with more severe destruction of the ganglion cells, with the preservation of but a few of these, with neuronophagia well advanced, most of the cells having disintegrated and undergone fatty changes; and the third stage, which was one of complete softening, with an absence of ganglion cells and macroglia, the only cells present being free, rounded, fat-filled Gitter cells. Common to all three stages was a great distention of the blood vessels and an absence of extravasation or diapedesis, thrombi or emboli. On the basis of their findings and after comparing them with those in a case with an organic vascular lesion, Hiller and Grinker concluded, "Stasis as the basis of the lesions in the pertussis case could be objectively demonstrated. The reason for the development of such stasis is not obvious except if it be, as in carbon monoxide poisoning, due to the action of a circulating noxious agent on the vessel walls."

Bonaba and Reyes,[39] in 1932, reported a patient with meningoencephalitis due to pertussis who made a complete recovery after the case was at first diagnosed as tuberculous meningitis. Grenet and Mourrut,[40] in 1933, reported on their experiences at the Bretonneau Hospital with convulsions occurring during whooping cough during the year ending October 1, 1932. Of 238 patients with pertussis, twenty-two or nearly 10 per cent had convulsions. All except three of these were less than 2 years of age. In nine cases the convulsions developed through the complication of pneumonia, in nearly one-half, otitis media was present, and in one acute mastoiditis was found. Several were encephalitic. The mortality for the twenty-two with convulsions was 90 per cent. Autopsies were performed in fifteen cases, and encephalitis was demonstrated in three of these, but the others showed in most instances merely congestion and edema of the brains. The authors believed that the theory that violent fits of coughing may result in cerebral hemorrhage is without basis of fact. Santillana,[41] in 1933, reported two fatal cases of encephalitis following pertussis. Gambirassi[42] in the same year reported a case with recovery. Ellison,[43] in 1934, reviewed a series of seventy cases of pertussis with convulsions. In the series there were just two terminations, death in forty-six and complete and rapid recovery in twenty-four. He mentioned the principal theories for the occurrence of convulsions in pertussis as being the apoplectic, the spasmophilic, the meningoencephalitic, the neurotoxic and the angiospastic. He gave greatest credence to the meningoencephalitic and the angiospastic theories.

Weisner,[44] in 1935, reported a case of pertussis encephalitis with recovery. Gianelli,[45] in 1936, reported two fatal cases but did not perform autopsies.

It is apparent from the foregoing review of the available literature on the subject that the neurological complications are not so infrequent but that they should always be watched for during the course of pertussis, particularly in young children. It is apparent also that a satisfactory explanation for their occurrence is not yet possible. It seems most likely that all cases are not attributable to the same causative factors and that only careful clinical and pathologic studies of the individual cases will disclose the etiology.

At the present time, the most likely explanation for the occurrence of neurological phenomena during whooping cough would appear to be one of the following:

1. Intracranial hemorrhage, which must be extremely rare in its occurrence.

2. Spasmophilia, which undoubtedly accounts for some cases of convulsions but which could hardly be thought to explain the more severe disturbances.

3. Functional vascular lesions resulting in stasis or prestasis, a theory which would offer a satisfactory explanation in some cases.

4. Encephalitis, either hemorrhagic or nonhemorrhagic, which, from available autopsy studies, would seem to be present in a large percentage of the cases.

SYMPTOMATOLOGY

The nervous complications of pertussis seldom appear during the catarrhal stage or even during the early part of the stage of convulsive coughing. Much more commonly they make their appearance at the peak of the stage of paroxysmal cough or even after it has begun to subside. Their onset may be explosive or they may appear insidiously. They are most prone to occur in very young children but may occur at any time during childhood.

The most common manifestation of neurological involvement in pertussis is the convulsion. This may appear during or after a seizure of coughing or may be independent thereof. The convulsion may be of short or prolonged duration, may be general in nature, or may affect only one side of the body or one extremity. The seizures are nearly always clonic in nature, and where they subside are likely to recur at intervals. In some instances they are followed by coma of longer or shorter duration or frequently by paralysis, which may be temporary or permanent. In those cases with coma there is likely to be accompanying irregularity or shallowness of respiration, vomiting, reflex changes, pupillary and eye muscle disturbances. Paralysis occurs most commonly in the form of hemiplegia, at first of flaccid and later of spastic nature. The paralysis may take the form of a paraplegia or less frequently a monoplegia. Instances of slowly advancing paralysis have been reported. In addition there have been described aphasias, disturbances of swallowing and phonation, tremors of various kinds, choreas, athetoses, and ataxias. In some instances these may occur without preceding convulsions.

Sensory disturbances have been described but are exceedingly rare.

Blindness of permanent or less often of temporary duration is not too uncommon. Deafness has been observed.

Instances of neuritis, polyneuritis, myelitis, and multiple sclerosis occurring in pertussis have been recorded, but a direct relationship seems doubtful.

Psychic disturbances are common. These may take the form of sleep disturbances, amnesias, anxiety neuroses, and mental depressions. In some cases, even without convulsions, there may appear more intense disturbances such as coma, delirium, melancholia, and the like. In the majority of cases, the last mentioned group make complete recoveries.

As late results of the neurological disturbances of whooping cough, epilepsy, mental retardation, spastic paralysis, or other disturbances may occur.

The aforementioned neurological disturbances may occur in a variety of combinations during the course of whooping cough, often presenting bizarre syndromes. From the point of view of prognosis or sometimes even diagnosis they may be difficult of interpretation. Their appearance should always be regarded seriously but, from the increasing number of complete recoveries following their occurrence reported in the more recent literature, they should not be regarded hopeless in the most severe instances, and every effort should be made to overcome them.

TREATMENT

In the case of convulsions, sedatives, lumbar puncture, calcium salts, dehydrating salts, and other agents may prove helpful. In cases with coma, the foregoing with tube feeding may be necessary. Paralyses should be treated with massage, passive exercise, and later muscle training and braces if necessary. Psychic disturbances should be treated with sedatives and psychotherapy. In treating the neurological complications of pertussis the treatment of the primary disease itself should not be overlooked. This, of course, includes the usual efforts to control the paroxysms of coughing, careful attention to the maintenance of nutrition, the use of vaccines, and convalescent serum. Unfortunately, no reports are available as to the results of treatment of cases of pertussis with neurological complications with convalescent serum. On theoretical grounds, if we assume that the pertussis bacillus liberates a toxin capable of acting as a noxious agent on either nervous tissue or the endothelial lining cells of the cerebral vessels, convalescent serum would appear to be the treatment of choice.

REPORT OF TWO CASES OF PERTUSSIS ENCEPHALITIS

CASE 1.—D. D., a white female child, 7 years of age, was first seen May 15, 1934, with the complaints of weakness, vomiting, and headaches. The child was at this time practically recovered from a moderately severe case of whooping cough which had begun two months before, with only mild and infrequent paroxysms of coughing still present. Family history and previous history were unimportant.

Present Illness.—About May 1, the child had begun to complain of frontal headaches and vomited after eating on several occasions. The headaches had continued and she had complained of weakness and had run slight fever of about 100° F. since.

Physical examination showed a thin, frail child with generalized muscular weakness, alert and active mentally. The pupils reacted normally. The eye grounds showed questionable fullness of the vessels but were otherwise normal. There was a profuse mucoid nasal discharge and there were engorged mucous membranes and turbinates. The neck was resistant to anterior flexion, and there was tenderness over the second spinous process of the spine. The blood pressure was 110/60. Tendon reflexes were all present, equal and active. There was a suggestions of a positive Babinski test on both sides. A tuberculin test and roentgenogram of the chest were both negative. The blood showed a slight leukocytosis.

Course.—The impression at this initial examination was that the child was suffering from a toxic arthritis of the spine secondary to a nasal sinus infection, and under decongestive nose drops and nasal suction there was considerable improvement so that ten days later the stiffness of the neck had disappeared. She was free of fever and headaches, and the weakness was not so prominent. She continued to improve until June 3, when she again became very weak, ataxic, and developed frequent attacks of projectile vomiting. On June 4 her mother noted that her left eye looked peculiar, and she complained of inability to see from that eye. Examination at this time disclosed a left internal strabismus, inequality of the pupils, and bilateral nystagmus. The left optic fundus showed dilated vessels and choking of the optic nerve. There was ataxia on sitting and standing, with a tendency to fall to the left. The tendon reflexes were unaffected.

At this time a diagnosis of cerebellar lesion, either tumor or abscess, was made, and this diagnosis was concurred in by a neurosurgeon called into consultation. Hospitalization for study was advised but was refused by the parents. During the next week the child continued to vomit forcefully in spite of dehydrating measures, and the other findings remained about the same. She then began to improve, her vomiting ceased, there was a slow decrease of the optic nerve choking, and loss of the ataxia. Improvement continued uneventfully and by June 30 she was completely recovered. She was observed at intervals during the next six months, with no return of symptoms.

CASE 2.—M. G., a white 9-month-old male child was first seen on March 8, 1936, during a convulsive seizure. Family history was unimportant.

Past History.—The patient had been breast-fed and always healthy up to the onset of the present illness. His birth had been normal. He had received cod-liver oil and orange juice.

Present Illness.—The patient had been well until February 1, when he developed a mild cough and upper respiratory symptoms. By February 10, the cough had become a "whoop" and a series of injections of pertussis vaccine was administered. The whooping cough became increasingly severe and he was soon vomiting most of the food taken and becoming quite weakened. On February 23, in the third week of the illness, he developed fever and increased respirations and bronchopneumonia was diagnosed. With this he ran a temperature elevation of 102 to 104° F. daily.

On March 6 his mother noted spasmodic twitchings of the facial muscles at intervals, the first sign of neurological disturbance. On March 8, in the sixth week of his illness, the child suddenly developed a severe, generalized clonic convulsion, which persisted for two hours in spite of sedatives and magnesium sulfate hypodermically. During the convulsions there were two periods of about five minutes each when respiratory effort was entirely absent and artificial respiration was

necessary. A lumbar puncture during the seizure revealed clear spinal fluid under slightly increased pressure with a cell count of 4, and normal sugar content. Following the convulsions, the child remained comatose, and, because of profound cyanosis and respiratory difficulty and irregularity, it was necessary to keep him in an oxygen tent for a period of ten days.

The child remained comatose for a period of altogether fourteen days, during which time there appeared bilateral nystagmus, irregularity of the pupils, and a spasticity of the right arm and leg. No eye ground changes or elevation of the blood pressure were present. On March 22, two weeks from the time of the convulsion, the child for the first time showed evidence of regaining consciousness. From that time on he continued to improve, with gradually increasing ability to use the right leg which had continued spastic, and to return to a normal state of mental clearness.

The child was slow in learning to walk but now, eighteen months after the illness, he uses the arms and legs well, shows no neurological deformities, and seems perfectly normal mentally.

DISCUSSION

The two cases presented here I believe are undoubtedly instances of pertussis encephalitis. The first case, occurring in an older child, was confusing because of the strict localization of the symptoms and signs to the cerebellum, and because of the mildness of the pertussis at the time of the appearance of neurological complications. The second case, while more typical of the usual course of pertussis encephalitis with recovery, is remarkable in that the severity of the symptoms apparently did not influence the completeness of recovery. Of course, the possibility of neurological sequelae in the form of epilepsy or mental backwardness later cannot be entirely excluded.

CONCLUSIONS

1. The literature dealing with the neurological complications of pertussis is reviewed.

2. The probable causes for neurological complications in pertussis, in order of frequency, are: (a) encephalitis, either hemorrhagic or non-hemorrhagic; (b) functional disturbances of the cerebral blood vessels; (c) spasmophilia; and (d) intracranial hemorrhage.

3. A brief resume of the symptomatology is given.

4. Two cases of pertussis encephalitis are added to those already reported.

I am indebted to Dr. T. L. Woodard of Dallas, Texas, for the reference of the first case and to Dr. W. L. Parker of Wichita Falls, Texas, for the second.

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WEIL'S DISEASE

Report of a Case Occurring in a Child

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WEIL[1] in 1886 described a disease characterized by sudden onset, general malaise, chills, fever, nausea, vomiting, myalgia and jaundice. Since the recognition of this condition by Weil, similar cases have been reported by other investigators. Noteworthy among these are the reports of Inada, Ito, and co-workers,[2] who in their arbeit with the Japanese variety of the disease, describe the etiological agent to be a spirochete. Noguchi in 1917 published an article verifying the work of Inada and classified the organism as *Leptospira icterohemorrhagiae.*

The disease has been repeatedly recognized in Germany, France, the Netherlands, Japan, and the East Indies. Particular attention has been called to the existence of the condition among troops during both the World War and other conflicts.

After the publication of the English version of the Japanese workers' findings in 1916, the condition became more widely recognized. Repeated case reports can be found in the literature from Germany, Italy, France, the Netherlands, and Japan. Particular attention is called to the existence of the condition among troops during the World War. Although the condition has attracted a great deal of attention in other countries for several decades, the first proved case of Weil's disease was not reported in the United States until 1922. In this year, Wadsworth and associates[3] reported a case affecting a laboratory worker who apparently acquired the disease through the accidental prick of a contaminated needle.

Since the report of this first case, there have been eleven additional cases reported in this country. The résumé of the American cases is admirably presented by Jehghers, Houghton, and Foley.[4]

The distribution of *Leptospira icterohemorrhagiae* is apparently world wide. These organisms have been repeatedly isolated from rats in both the American and European continents. The predisposing features of occupation and environment have been repeatedly noted by the early and present investigators. Individuals working in damp, rat-infested areas are more prone to acquire the disease than other persons. Weil's disease is particularly prevalent among miners, sewer workers, bargemen, garbage workers, and fish cutters. In at least two cases the condition has been recognized as a laboratory infection (Wadsworth and co-workers[3] and Kortoff[5]).

Although rats are considered the principal source of the infection, Wirth[6] believes that dogs and other animals act as carriers of the disease. The above investigator has been able to show that dogs can be infected by *Leptospira icterohemorrhagiae*. Furthermore, Schuffner[7] was able to show the *Leptospira canicola* or the canine strain of leptospira can infect man. Wirth, although not making specific reference to the cases, states that human infection of leptospirochetosis has been known to be acquired from infected dogs.

The following case of Weil's disease is reported not only because of the few cases reported in the United States but also because the source of the infection has been proved.

CASE REPORT

CASE 1.—D. S. (D-1300), white, male, three years of age.

Past History.—Negative except for frequent attacks of colds and croup.

Present illness began Jan. 28, 1938, when the child vomited and the temperature rose to 102° F. rectally. Physical examination at this time was negative, and the condition was thought to be the beginning of a respiratory infection similar to those the child had previously. The following day the child was markedly improved, and the mother telephoned saying she believed the child was almost well. On Feb. 1, 1938, the child was seen because the mother noticed he was drowsy and did not seem quite as well. She remarked that Jan. 30 and 31, 1938, he seemed entirely recovered.

Physical examination on Feb. 1, 1938, revealed a well-developed, well-nourished, male child. There was a slight icteric tint to the conjunctivae. The temperature was 99.6° F. rectally. Pulse was 90; respiration, 22. The balance of the examination was negative. A stool passed at this time was normal in appearance. The urine was dark and gave a positive bile test.

At this time (Feb. 1, 1938) a diagnosis of Weil's disease was made clinically based upon the onset with vomiting on January 28, 1938, the appearance of jaundice on Feb. 1, 1938, and the history obtained at this time that the child's pet dog had been ill two weeks previously. The dog was a male Scottie who spent most of his time outdoors chasing rats. He had become ill about Jan. 15, 1938, with vomiting and fever, and on Jan. 17, 1938, developed jaundice. The child had been with the dog from Jan. 15 to 18, 1938, and handled him a great deal until he was sent to the veterinarian on January 18. After a period when the veterinarian did not expect him to live, the dog finally recovered and was brought home on Feb. 1, 1938.

From February 2 to 10 the icterus became progressively more severe. The child's temperature remained 99.6° F. rectally throughout the period, and his appetite was only slightly impaired. He felt fine, and it was difficult to keep him in bed. The stools remained practically normal in appearance throughout the period. The liver slowly enlarged during this interval, but the spleen was not palpable.

On Feb. 11, 1938, the temperature rose to 103° F. rectally, the child became drowsy; the icterus became more intense; and the liver enlarged to extend 10 cm. below the costal margin.

On February 12 the child's temperature rose to 104° F. rectally, and he became slightly irrational. The following morning the child was slightly delirious. The temperature at this time was 99.6° F. rectally. The child was admitted to the Children's Hospital of Michigan at noon Feb. 13, 1938. At this time Dr. Thomas B. Cooley saw the child in consultation. The rectal temperature remained below 99.6° F. throughout the day. The child was comatose from the time of admission.

On the following morning, Feb. 14, 1938, the rectal temperature rose from 99.6° F. at 6:00 A.M. to 102° F. at 8:00 A.M., 104° F. at 11:00 A.M., and death occurred at 12:45 P.M.

Laboratory Data.—Feb. 13, 1938. Hemoglobin, 17 gm.; red blood cells, 4,670,000; white blood cells, 11,450; polymorphonuclears, 68 per cent; small mononuclears, 32 per cent.

Guinea pig inoculation of the child's blood and urine showed spirochetes in the blood upon examination of the guinea pig. The dog was taken to Herman Kiefer Hospital, and blood and urine inoculations from the dog were made in guinea pigs. Blood from both the dog and child was sent to the National Institute of Health, and agglutinations of 1 to 30,000 against *Leptospira icterohemorrhagiae* were reported. Tissues removed from the child at post-mortem examination were inoculated into guinea pigs and produced jaundice on the second passage. Spirochetes were found in the urine of the guinea pigs dying of jaundice. Sections of liver tissue showed spirochetes upon microscopic examination.

SUMMARY

A case of proved Weil's disease occurring in a child is reported. This is the first proved case which has occurred in Detroit and is of interest not only because of its rarity, but especially because the source of infection (the pet dog) was definitely proved.

While Weil's disease is not a common cause of jaundice in the United States, its occurrence should be kept in mind whenever jaundice of hemolytic origin is encountered. Specific serum therapy is reported to give encouraging results and should be obtained from the National Institute of Health whenever a case is diagnosed, since this is the only therapy of specific value known.

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NIEMANN-PICK'S DISEASE

Report of Three Cases in One Family

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ALTHOUGH Niemann-Pick's disease has always been considered a congenital, familial, and constitutional disease, only four of the forty-two cases described in the literature are strictly familial. Knox, Wahl and Schmeisser[1] described the disease in two sisters. Stransky[2] reported the condition in a brother of Dienst's[3] patient. Nordmann[4] observed the malady in the brother of the patient whose case was described by Corsan, Oberling, and Dienst.[5] Winter[6] described the condition in two sisters.

However, there are several doubtful familial cases in the literature. Siegmund[7] stated that a sister of his patient died in the first year of life from an enlarged liver and spleen. Dienst and Hamperl[8] reported that a younger sister of their patient died at the same age with symptoms, the mother said, similar to those of the brother. Hamburger[9] reported that another child in the family died with a large liver and spleen. In Berman's case,[10] a sibling died with a large abdomen, cause unknown. The first child in the family of Dienst's patient[3] died suddenly and the autopsy revealed a large liver and spleen. A sister of Winter's two patients[6] died with a large liver and spleen and secondary anemia.

We have had under our observation three cases of Niemann-Pick's disease occurring in one family. There were no normal children in this family. As far as we know, this is the first time that such an occurrence has been described.

The parents of these children were first cousins, and the parents of the mother were first cousins. Both parents were Jewish and were born in Russia.

Case 1.—The first child was seen in 1927. The clinical aspects of this case were discussed in a previous report,[11] and the pathology of the spleen was described by Dr. Lederer.[12]

Case 2.—The second child was admitted to the pediatric service of the Jewish Hospital on April 4, 1929, at the age of 3½ months, with the complaint of vomiting of eight weeks' duration and failure to gain weight. Just before the onset of vomiting, the child had had an upper respiratory infection, at which time the enlarged spleen was first felt by the attending physician.

Physical examination at the time of admission revealed the following: The patient was a well-developed, but somewhat undernourished white female infant who did not appear acutely ill. The height was 22 inches. The head measured

From the Department of Pediatrics of the Jewish Hospital.

15 inches in circumference; the chest, 15¾ inches; and the abdomen 14 inches. The skin showed a slate-blue discoloration over the left buttock and lower sacrum, resembling the so-called Mongol spot. There were shotty cervical, axillary, and inguinal lymph nodes. The anterior fontanel measured 6 by 6 cm. The posterior fontanel was still just barely open. There was no craniotabes. The eyes were normal, and there was no cherry-red spot in either macula. The costochondral junctions were palpable, but not enlarged. The heart and lungs were negative. The abdomen was distended and full. The liver was felt 7.5 cm. below the costal margin at the level of the umbilicus. The spleen was felt 5.5 cm. below the costal margin and was firm in consistency.

The laboratory findings: Repeated urine examinations were negative. Nose and throat cultures were negative. Vaginal smear was negative. Tuberculin tests were negative to 5 mg. Schick and Dick tests were negative. The Wassermann and Kahn tests were negative. The bleeding time was 1 minute, 30 seconds. The coagulation time was one minute. X-ray films of the chest showed a slight exaggeration of the perivascular markings in both lung fields. X-ray studies of the skull and long bones showed no evidence of pathology. Chemical determinations on blood serum revealed the following values: Calcium, 10.4 mg.; inorganic phosphorus, 4.8 mg.; cholesterol, 240 mg.; total nitrogen, 1.12 gm.; total phosphorus, 6.81 mg.; Nonprotein nitrogen, 29.3 mg.; albumin, 0.716 gm. (4.47%); globulin, 0.375 gm. (2.34%); albumin-globulin ratio, 1.91; total base, 152 milliequivalents per 100 c.c. of serum. The carbon dioxide was 16.9 volumes per cent on the day before death. The blood picture showed the erythrocyte count to be between 2,950,000 and 4,710,000. The leucocyte count varied between 9,800 and 11,600, with between 44 and 63 per cent polymorphonuclear cells. Between 16 and 39 per cent of the monocytes were vacuolated. The platelet count was 140,000.

The clinical course in the hospital: The temperature remained normal for the first ten days after admission and then became elevated to 103° F. due to dehydration. From then on it fluctuated between 100° and 102° F. for two days, then between 102° and 106° F. until death. The child did not take her feedings well, vomited frequently, and slowly lost weight. Her formula was changed to thick cereal feeding, but this, also, was not well tolerated. Hypodermoclyses were administered, to combat the dehydration, but the child continued to lose ground steadily. The liver and spleen were still enlarged, and the skin was dry and wrinkled. A subicteric tinge of both the skin and the sclerae developed and gradually became more intense. The respirations became rapid, and a sweetish odor was noted to the breath. With a carbon dioxide of 16 volumes per cent at this time, a diagnosis of acidosis was warranted. Diarrhea developed and increased the loss in weight, the child having lost 2 pounds since admission (two and one-half weeks). Two transfusions were administered, but no improvement resulted. The stools began to show undigested food. The child became moribund on the following day. On April 25, 1929, just three weeks after admission, the child expired.

The necropsy was performed by Dr. Lederer who reported as follows: Most of the pathology was in the liver, spleen, and bone marrow. The spleen measured 8 by 5 by 2½ cm. and weighed 48.5 gm. It was smooth, hard and mottled pink, yellow, red and blue in an irregular fashion. Its normal shape was preserved. On section the surface was smooth, and the color was a mixture of varying sized areas of yellow, red, and pink. The follicles were easily distinguished but appeared to be diminished in number. The vessels were not unduly prominent, and the surface was dry, presenting a somewhat glazed appearance. The splenic artery and vein appeared normal. There were no lymph nodes visible or palpable. In the gastrosplenic omentum there was a spleniculus, 3 mm. in diameter. The microscopic study showed a complete absence of normal splenic structure. The follicles

were completely absent and the pulp was replaced by large foam cells that were found throughout. The sinuses, also, were filled with similar cells. Some sinuses contained red blood cells.

The liver weighed 239 gm. The enlargement was uniform, being present in the left as well as in the right lobe. The shape was that of the normal. The organ presented a waxy appearance. The surface was smooth. The color was a uniformly bright pale yellow, glistening, and mottled occasionally with pink and red. The consistency was fairly hard. On section it cut with resistance, showing a uniformly bright yellow color with a streaking of red in patches. The gall bladder was pale green and distended with thin greenish yellow bile. The bile passages were patent and normal. The papilla of Vater was normal. Microscopically the entire parenchyma was made up of large foam cells which appeared granular with nuclei. There were only a few liver cells remaining, and these showed granular degeneration.

One femur, a vertebra, and a rib were studied. Grossly, they appeared normal. The marrow of the shaft of the femur was abundant, bright red in color, and semifluid in consistency. Microscopic study of the bone marrow revealed hyperplasia. Megakaryocytes were normal in number. Foam cells were abundant, large in size, and had definite cell membranes. The cytoplasm consisted of a spongy material, was eosinophilic, and contained a granular nucleus. The cells were 15 to 20 microns in diameter. The myeloid and the erythrogenetic elements were separated by these foam cells.

The microscopic study of the adrenals revealed many foam cells between the vessels. The smears from the splenic and portal blood showed many large lipoid-laden cells.

The anatomical diagnosis was histiocytosis of the liver, spleen and bone marrow.

CASE 3.—The third child was born on Sept. 16, 1932. He was seen in the outpatient department of the Jewish Hospital on Feb. 21, 1933, at the age of 5 months, with the chief complaint of vomiting. He did not take his feedings well. He was born at term, following a normal labor. He had made normal progress until two weeks before admission to the clinic, when he began to vomit. Physical examination at this time revealed a well-developed male infant with a large abdomen. His weight was 13 pounds 7 ounces; and his height was 26 inches. The head measured 16½ inches in circumference; the chest, 16½ inches; and the abdomen, 18 inches. The anterior fontanel was open, measuring 2 by 2½ inches. There was no craniotabes. There were large glands on both sides of the neck. The heart and lungs were negative. The spleen was enlarged, reaching to the symphysis, and the notch was palpable. The liver was felt 2 fingerbreadths below the costal arch. The knee jerks and the ankle jerks were present. The ophthalmoscopic examination was negative. The child did not attempt to sit up. The blood picture at this time was: Hemoglobin, 71 per cent; erythrocytes, 4,600,000; leucocytes, 22,000, with 34 per cent polymorphonuclears and 66 per cent lymphocytes. Hospitalization for further study was advised, but that was refused by the mother.

The child was again seen in the clinic on March 27, 1934, when he was 18 months old. In the intervening time he had not taken his feedings well and had had frequent attacks of vomiting. He also had had repeated upper respiratory infections. At this time, his weight was 17 pounds, 3 ounces; and his height was 30 inches. He had gained only 60 ounces in thirteen months. He could not lift up his head or sit up. Physical examination showed evidence of loss of weight. The musculature of the extremities was poorly developed. In contrast to this, there was a very large abdomen due mostly to the enlargement of the spleen and liver. The liver edge was palpable at the level of the umbilicus. The lower edge of the

spleen was lost in the pelvis. The posterior border was in the axillary line. Its surface was smooth. It was freely movable and notching was noted. The rest of the abdomen was soft and not tympanitic. The muscles were not tense. The anterior fontanel was still open and measured 1½ by 1½ inches. The posterior fontanel was closed. The bosses were prominent, and the tip of the head was flattened. The inguinal, epitrochlear, and peritonsillar lymph nodes were all palpable and shotty. There was some resistance to extension of the legs. It was difficult to obtain the knee jerks, but the ankle jerks were present on both sides. Ankle clonus was absent. The Kernig and the Babinski phenomena were not present. Examination of the genitals revealed both testes to be in the inguinal canals, but they could be moved into the scrotum. Ophthalmoscopic examination revealed a cherry-red spot in the macula of the left eye. Hospitalization was again advised and again refused by the mother.

The child did not do well during the last four months of his life, having repeated attacks of vomiting and upper respiratory infections. Bronchopneumonia finally developed, and the child expired two days after the onset, just four months after he was last seen at the hospital.

Repeated study of blood smears always showed vacuolization of the mononuclear cells.

In July, 1934, the mother was admitted to the obstetric service of the Jewish Hospital. At this time she was in the third month of gestation. She had been referred to the hospital for a therapeutic abortion. It was the opinion of the pediatric and medical staffs that a therapeutic abortion should be done, but the obstetrician and the endocrinologist could find no indication for such a procedure. She remained at the hospital for ten days and then was discharged at her own request. A therapeutic abortion was done later, elsewhere.

During her stay in the hospital, she was examined thoroughly by the members of the various services. Physical examination was negative except for slight fullness of the thyroid and widely spaced teeth. X-ray films of the skull showed a sella turcica of normal size. The clinoid processes were intact. The electrocardiograph showed dominant sinus rhythm with low voltage. The basal metabolic rate was −7 per cent. The Wassermann and Kahn tests were negative. Examination of the urine was negative. Blood chemistry studies revealed the following: sugar, 84 mg.; creatinine, 1.0 mg.; urea nitrogen, 9.1 mg. per 100 c.c. of blood. The blood picture showed 4,050,000 red blood cells, 82 per cent hemoglobin, and 8,550 white blood cells.

COMMENT

The clinical pictures in these cases are typical of other cases of Niemann-Pick's disease described in the literature. The disease is a congenital, familial, constitutional disorder of lipoid metabolism that occurs mainly in Jewish female infants of Eastern European extraction. It manifests itself early in life and is characterized by feeding difficulties (refusal of food and vomiting), a large spleen and liver, generalized brownish discoloration of the skin, occasionally with Mongol spots, moderate leucocytosis with vacuolization of the monocytes, moderate anemia, an increase in the lipoid constituents of the blood, and repeated upper respiratory infections with bouts of fever. In some cases a cherry-red spot is seen in the fundus. Physical and mental retardation and progressive deterioration with a fatal termination from progressive cachexia or intercurrent infection before the end of the second year

represent the usual course of the disease. The vacuolization of the monocytes, described by Abt and Bloom,[13] and by Bloom[14] and others, is an important diagnostic sign.

The characteristic lesion from the pathologic viewpoint is an infiltration of the spleen, liver, bone marrow, lymph nodes, suprarenals, thymus, and, to a lesser extent, practically all of the organs and tissues of the body with large lipoid-laden phagocytes or histiocytes. These are called foam cells because of their vacuolated appearance. The vacuoles contain lipoid droplets and lecithin.

Sobotka, Epstein and Lichtenstein[15] made a study of the lipoid content of the liver, spleen, and brain. They found that the increase in lipoids was due to large amounts of phosphatids and cholesterol esters.

The nature of this lipoid disturbance in which the body is flooded with phosphatids and cholesterol esters is not clearly understood. Some investigators believe that the reticuloendothelial system is not functioning normally in the metabolism of lipoids; others, that the cells of the liver are not functioning properly; and still others, that the fault lies with the endocrine glands.

Of late, considerable interest has been focused upon the relation of Niemann-Pick's disease to amaurotic family idiocy (Tay-Sachs' disease). The pathognomonic sign in amaurotic family idiocy is the cherry-red spot in the macula. This sign is also present in some cases of Niemann-Pick's disease and is absent in others. Two of our three cases showed this cherry-red spot in the macula.

Recently, Pick and Bielschowsky[16] and Bielschowsky[17] alone made studies of post-mortem material of cases of amaurotic family idiocy and of Niemann-Pick's disease. As a result of their studies, they suggested an intimate relationship between the two conditions. The degenerative changes in the central nervous system that are seen in Tay-Sachs' disease are also present in Niemann-Pick's disease. In view of the essentially analogous abnormality of lipoid metabolism and pathologic changes in both conditions, many investigators are convinced of the identical nature of the two diseases. They advocate that amaurotic family idiocy should be regarded as a partial manifestation of Niemann-Pick's disease—partial, in that the foam cells are found in the central nervous system alone, whereas in Niemann-Pick's disease, they are found throughout the entire body and especially in the reticuloendothelial system.

SUMMARY

1. Three cases of Niemann-Pick's disease occurring in one family are presented, together with their clinical, laboratory and pathological findings. Laboratory studies done on the mother are also presented.

CLINICAL SUMMARY OF THREE CASES OF NIEMANN-PICK'S DISEASE

E. L.	B. L.	A. L.
Sex: Female	Female	Male
Age at onset: 4 months	6 weeks	4½ months
Skin: Brownish discoloration with Mongol spots	Brownish discoloration with Mongol spots	Brownish discoloration with Mongol spots
Lymph glands: Cervical lymph nodes enlarged	Generalized lymph node enlargement	Generalized lymph node enlargement
Eyegrounds: Cherry-red spot in the macula	Negative	Cherry-red spot in the macula
Red blood cells: 2,720,000	2,950,000	4,600,000
Hemoglobin: 62%	55%	71%
White blood cells: 12,600	11,600 with vacuolization of the monocytes	22,400 with vacuolization of the monocytes
Platelets: 220,000	140,000	Platelet count not done
Blood cholesterol: 137.5 mg. per 100 c.c. whole blood	240 mg. per 100 c.c. whole blood	Not done
Pathology: Spleen showed many foam cells	Spleen, liver and bone marrow showed many foam cells	
Age at death: 15 months	4 months	22 months

2. A cherry-red spot was seen in the macula of two of the patients, and in one it was absent.

3. Statistically, the probability of the accidental incidence of three cases of Niemann-Pick's disease in one family is once in 1,000,000,000 cases.

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THE ROENTGENOLOGIC DEMONSTRATION OF ESOPHAGEAL VARICES AS A DIAGNOSTIC AID IN CHRONIC THROMBOSIS OF THE SPLENIC VEIN

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IN RECENT years a number of reports dealing with the symptom complex of gastric hemorrhage, alterable splenomegaly, leucopenia, and anemia have appeared in the literature.[1] It is generally accepted that this symptom complex results from an obstruction in the portal or splenic veins which may be due to a thrombophlebitis of the vessels, narrowing of the splenic vein, congenital malformations of the portal or splenic veins, pressure on the veins from without, or sclerosis of the vessel walls. As a result, a collateral circulation is established, the extent of which depends upon the degree of obstruction. Esophageal and gastric varices result from overfilling of these collateral veins which attempt to carry the blood away from the engorged spleen. As is well known, the spleen, in addition to its hemolytic activities, acts as a blood reservoir for the circulation, and any interference with the return flow will produce a tremendous increase in the size of this organ unless a competent collateral circulation is rapidly established. Eventually, however, the collateral circulation is taxed to such an extent that rupture of these varices occurs, and it is when these varices rupture that the characteristic gastric hemorrhage takes place.

Various reports[2] indicate that chronic thrombosis of the splenic vein can be and has been recognized before operation or necropsy studies. Recognition, however, was possible only after gastric hemorrhage had occurred. We believe that it is of great importance that this disease be recognized early, i.e., before the occurrence of hematemesis, because the institution of proper treatment, namely, splenectomy, omentopexy, and ligation of the coronary veins, early in the disease will prevent, first, a dangerous and often fatal hemorrhage, and second, it may prevent progression of the process with its resulting irreparable damage to the liver. Of fifteen patients observed by Smith and Farber, six died of uncontrollable gastric hemorrhage.

We believe that chronic thrombosis of the splenic vein can be recognized before gastric hemorrhage occurs, provided the disease is kept in mind and esophageal varices are looked for in a case of unexplained splenomegaly. In the two cases reported here the esophageal varices

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were demonstrated after the occurrence of gastric hemorrhage and after the diagnosis had been made clinically; it is obvious, however, that, had these children been seen before the hemorrhage and an enlargement of the spleen observed, roentgenologic examination of the esophagus for the presence of varices would have shown them to be present and would have established a diagnosis. Demonstration of esophageal varices by means of roentgenograms was first reported by Wolf[3] in 1928. Since then a number of reports dealing with the demonstration of esophageal varices in cirrhosis of the liver and in thrombosis of the splenic vein have appeared in the literature.[4] The technique employed by us was as follows: 1 ounce of barium sulfate, ½ ounce of powdered acacia, and 2 ounces of water were mixed forming a thin gruel. One-half ounce of this mixture was given, and the patients were examined fluoroscopically in the erect and prone positions. The latter proved to be more satisfactory, as the normal esophageal flow is retarded in the recumbent position. Spot films may be taken at any time.

With the patient in the right anterior oblique posture the barium mixture flows freely through the tube, usually hesitating somewhat at the cardia, so that the lower third, at the proper time, can be visualized as a smooth conical tube tapering inferiorly to a fine point at the esophageal hiatus.

When varices are present, there is usually delay, the conical point is lost, and the smooth normal markings are replaced by irregular defects, varying in size from a lentil to that of a small hazelnut. There are negative shadows produced by the crest of the engorged veins, the barium resting in the trough of the vermicular varicose waves. Rugal markings are lost. There are changes in appearance at varying times, depending upon the degree of venous engorgement and the position of the barium gruel at the moment of projection. It is for this reason that repeat studies are strongly advised. Best radiograms are usually obtained during forced expiration, since inspiration tends to elongate, strip, and flatten the venous channels.

The pictures obtained in both cases show the varices clearly (Figs. 2 and 3). Fig. 1 shows a normal esophagram and demonstrates the marked difference as compared with the roentgenograms in the two cases under discussion.

CASE 1.—B. F., a white female, 2½ years old, was brought on Nov. 1, 1933, because of severe gastric hemorrhage which had occurred the night before. The father was suffering from tuberculosis, and the mother was under treatment for chronic heart disease; two brothers were living and well. The past history was not significant. On Oct. 28, 1933, the child complained of abdominal pain and refused food; on the following day, however, she appeared well. Three days later she vomited breakfast and again refused all food for the remainder of the day. At eight o'clock in the evening she had a profuse hemorrhage from the mouth; the bleeding

occurred suddenly and was not accompanied or preceded by either vomiting or coughing. The temperature was not elevated, and there was no complaint of pain. The child became pale immediately after the hemorrhage. The next day she was seen, and physical examination revealed the following (only the essential findings are given): The sensorium was clear, and the nutritional status was good. There was marked pallor of the skin. The mucous membranes of the conjunctiva and mouth were pale; petechiae and hemorrhages were not seen. Physical and fluoroscopic examinations of the lungs were negative. The abdomen was large and protuberant, and there was dilatation of the superficial veins of the lower part of the anterior surface of the thorax and the upper portion of the abdomen. The spleen could be felt one

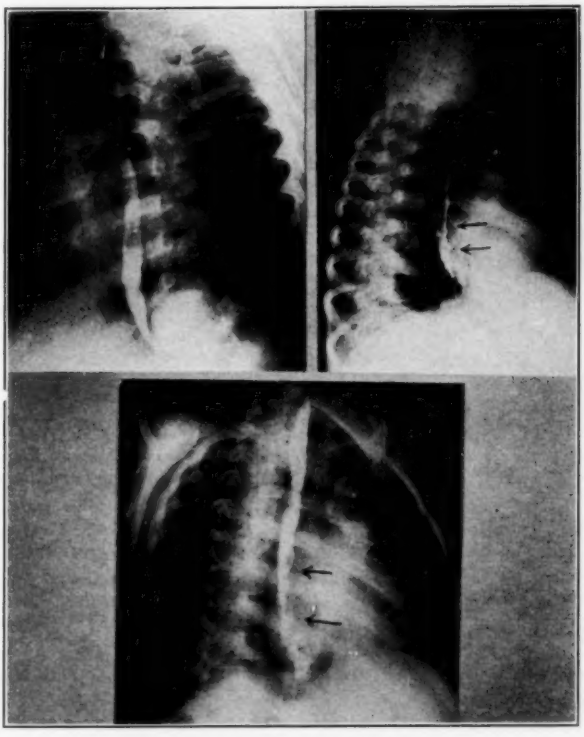

Fig. 1.—Roentgenogram of a normal esophagus.

Fig. 2.—Case 1. The esophagus is irregular in configuration and has a worm-eaten appearance throughout its course, particularly in its lower half.

Fig. 3.—Case 2. The esophagus shows irregularities in its lower half, particularly that portion between the hiatus and the cardiac orifice.

fingerbreadth below the costal margin; there was no enlargement, however, of any of the lymphatic glands. The capillary resistance test was negative; the hemoglobin (Sahli) was 20 per cent, and the white blood count was 3,800, with 70 per cent lymphocytes. A diagnosis of thrombosis of the splenic vein was made and hospitalization was advised.

The patient was admitted to the hospital on the afternoon of the same day. Examination of the blood showed 1,900,000 red blood cells, 22 per cent hemoglobin (Sahli), and 4,200 white blood cells of which 41 per cent were neutrophils, 51 per

cent lymphocytes, and 2 per cent myelocytes. The bleeding and coagulation times were normal, and the platelet count was 260,000. Two hundred cubic centimeters of whole blood were given directly into the vein. On the following day the spleen could be felt four fingerbreadths below the costal margin. This was considered important confirmatory evidence of the diagnosis. On November 5 a blood count showed 2,350,000 red cells and 4,100 white cells, of which 56 per cent were neutrophiles, 42 per cent lymphocytes, and 2 per cent monocytes. The hemoglobin content was 49 per cent (Sahli). The presence of leucopenia, even after a severe hemorrhage, and its persistence after transfusion were also considered additional confirmatory findings. On this day surgical intervention was advised, and it was suggested by the surgeon that ligation of the splenic vessels be performed instead of splenectomy, and on November 6 the child was operated on. A small amount of free sanguineous fluid was found in the abdominal cavity. The splenic vein was thrombosed from the spleen to the greater curvature of the stomach. The splenic veins and artery were ligated and the wound was closed. On the following day the temperature became elevated, and there were evidences of a pneumonic process at the base of the left lung; the child, however, did not look very ill. The process gradually subsided, and the child recovered after two and one-half weeks.

Examination of the blood eleven weeks after the operation showed 3,100,000 red cells, 6,000 white cells with 29 per cent neutrophils, 67 per cent lymphocytes, and 4 per cent myelocytes. The hemoglobin content was 65 per cent and the platelet count was 300,000. The bleeding time was three minutes and the coagulation time, seven minutes. In other words, leucopenia with a preponderance of lymphocytes was still in evidence. The spleen was no longer palpable. On Feb. 10, 1934, the white blood count was 6,000 with 64 per cent polymorphonuclear leucocytes; the platelet count was 320,000; the bleeding and coagulation times were normal.

On Nov. 4, 1935, one year after the splenectomy, another gastric hemorrhage occurred. The hemoglobin was reduced to 76 per cent, but no transfusion was given. On Nov. 13, 1937, the child again vomited a large amount of blood; the blood loss was severe enough to require hospitalization and a transfusion of 350 c.c. of blood. On November 17 another severe hemorrhage occurred, and a transfusion of 350 c.c. of whole blood was given. On December 2 the total cholesterol was 211 mg. per cent, the free cholesterol 128 mg. (60 per cent), and the cholesterol esters 84 mg. (39 per cent), evidence of disturbed liver function. A galactose test done on December 6 showed that 8.74 gm. of galactose were excreted at the end of four hours; (with normal liver function 3 gm. or less are excreted in four hours).

On December 7 a roentgenogram of the esophagus (Fig. 2) showed that the esophagus was irregular in configuration and had a worm-eaten appearance throughout its course, but particularly in its lower half. On November 17, immediately after the hemorrhage, examination of the blood showed 1,890,000 red cells, 35 per cent hemoglobin (Sahli), and 10,300 white cells; of these 72 per cent were neutrophils. On November 24 the number of red cells rose to 2,560,000 and the hemoglobin content to 49 per cent; the leucopenia was again in evidence, the white blood count being 5,900 with 57 per cent lymphocytes; the platelet count was 230,000. The phosphatase content of the blood was determined on Dec. 2, 1937, and it was found to be twenty-eight units.

CASE 2.—L. B., a white female, 9 years old, was admitted to the hospital on March 16, 1938, because of a severe gastric hemorrhage which had occurred that afternoon. The patient's past history was negative except for the fact that in early childhood she had measles, chicken pox, and mumps. In August, 1937, the parents were told that the child suffered from anemia, and treatment was instituted for it. Two days before admission to the hospital it was noticed that the child was paler

than usual, but she appeared normal on the following day. On the day of admission the patient vomited huge, dark red clots three times but had no other symptoms except extreme weakness.

Physical examination revealed a thin, pale child with a slight enlargement of the spleen which could be felt one-half fingerbreadth below the costal margin. There were no elevation of temperature, no petechiae on the skin or mucous membranes, and no ecchymotic areas. The abdomen was soft, moderately retracted, and not tender; the heart was normal but the rate was rapid, 150. A tentative diagnosis of chronic thrombosis of the splenic vein was made and procedures were carried out to rule out the presence of a gastric or duodenal ulcer and thrombocytopenic purpura. The patient was given an indirect transfusion of 300 c.c. of citrated whole blood on the same day. On March 18, two days after admission, it was noticed that the spleen could be felt three fingerbreadths below the costal margin; the edge was firm and notched. A definite diagnosis of splenic vein thrombosis was now made, and an esophagram was done to determine the presence of varices. Roentgenologic examinations of the esophagus on March 20 and again on March 23 showed irregular digitations in the lower half of the esophagus, including that portion between the hiatus and the cardiac orifice. Roentgenologic examination of the gastrointestinal tract showed no abnormalities.

Examination of the blood before operation, on admission, i.e., the day after the hematemesis, showed the red blood count, 1,600,000; the hemoglobin content, 34 per cent (Sahli); the white blood content 8,600 with 74 per cent neutrophils; the platelet count was 39,800; the coagulation and bleeding times, five and two and one-half minutes respectively. The Mantoux test was negative; the blood chemistry was normal; the Wassermann and Rosenthal tests were negative. On March 18 the red count rose to 2,430,000, and the hemoglobin increased to 55 per cent; the white blood cells were only 7,000 in number with 70 per cent granulocytes; the platelet count was 75,000. Examination of the bone marrow showed normal findings. The icteric index was 6.6 units and the van den Bergh test gave a faint positive direct reaction. Several tests for increased fragility of the red cells were negative; hemolysis began at 0.375 per cent sodium chloride and was complete at 0.3 per cent. On March 31 the number of white blood cells had dropped to 3,600; the number of platelets was still low, 35,000.

The galactose test was negative; only 0.1632 gm. of galactose was excreted at the end of four hours. On March 24 five minims of a 1:1,000 solution of adrenalin chloride were injected subcutaneously, and within ten minutes the spleen could be felt only one-half fingerbreadth below the costal margin, whereas just before the adrenalin was injected it was palpable at three fingerbreadths below the rib. Unfortunately, the time in minutes for the spleen to return to its former size was not determined.

On April 1 the patient was again given a transfusion of 200 c.c. of citrated blood preparatory to operation which was done on the following day. At the time of operation it was noticed that a small amount of free fluid was present in the peritoneal cavity. The splenic pedicle was broad, and the splenic vein had the appearance of a thick, white fibrous cord. The spleen was thick, larger than suspected from the physical examination, and considerable difficulty was encountered in its removal because of multiple adhesions to the diaphragm and lateral peritoneum. The liver was inspected and was found to be small and cirrhotic. This was somewhat surprising in view of the fact that the liver function tests done before operation all showed normal values. It had been intended to tie off the coronary veins in addition, but the child's general condition was so poor that only the omentopexy was done. The patient was given another transfusion of 200 c.c. of whole blood while on the table, as soon as the operation was completed. Twenty-four hours later evidences of massive collapse of the lung were present, and the child's general condition be-

came grave. The presence of labored rapid breathing, cyanosis, and orthopnea made the use of an oxygen tent necessary for several days. The child gradually began to improve after five days and eventually recovered. However, in view of the fact that the liver was cirrhotic at the time of operation, the outlook in this case, too, is regarded as grave.

On April 5 the white cells rose to 13,800, and the polymorphonuclear cells were 83 per cent; the increase in the number of white cells was probably due to the post-operative reaction and to the massive collapse of the left lung. Interestingly enough, the platelet count at this time increased only slightly; there were 132,500 platelets. On April 16 the platelet count had dropped to 85,200; the white count, however, still showed 13,000 cells, of which 80 per cent were neutrophils. By May 1 the platelet count rose to 630,000.

The total cholesterol, free cholesterol, and cholesterol esters were determined on April 8 and 13, six and eleven days respectively after operation. The values obtained were as follows: April 8, 1938, total cholesterol, 226 mg. per 100 c.c. blood; free cholesterol, 130 mg. (57 per cent); cholesterol esters, 96 mg. (42 per cent). On April 13, 1938, values obtained were: total cholesterol, 169 mg. per 100 c.c. blood; free cholesterol, 68 mg. (40 per cent); cholesterol esters, 101 mg. (59 per cent). On April 13 the Takata-Ara test was positive.

On April 22 a bromsulphalein test showed that 10.5 per cent of the diet was retained at the end of one hour. In other words, liver tests done before operation showed normal function, whereas those done after operation showed disturbed function.

Examination of the spleen by the pathologist (Dr. Ravid) was as follows:

Gross Description.—The spleen was moderately enlarged, and weighed 250 gm.; it measured 12 by 10 by 5 cm. On section the cut surface was meaty-red in color, semielastic in consistency, and contained numerous minute pinpoint-sized follicles, which were uniformly distributed throughout the pulp. About forty-five follicles could be counted per square centimeter.

A number of gaping distended sinuses and veins were seen, especially at the hilar portion. The connective tissue trabeculae were prominent, increased in number, and appeared as irregular strands throughout the pulp. Numerous serial sections were made, and no other abnormalities, such as infarctions, tumefactions, or necrosis, were found grossly.

Microscopic Examination.—The salient histologic features were as follows:

1. The capsule was moderately thickened, and the trabecular cords were increased in number and thickness.

2. The Malpighian corpuscles were also increased in number, well defined, and stood out prominently by the component lymphocytes. Their central arterioles were ill defined and partly hyalinized.

3. The lymph sinuses were prominent and increased in number, with irregular lumina which gaped as though the organ had been previously perfused. They contained erythrocytes, lymphocytes, and neutrophils; the latter appeared increased in number.

4. The intervening supporting stroma in the cortex, as well as in the pulp, showed marked hyperplasia of the reticular fibers which appeared in many places as compact fibrous cords and contained a moderate number of reticular cells and histiocytes. In fact, the entire picture was that of a chronic hyperplastic splenitis.

Pathologic Diagnosis.—Chronic hyperplastic splenitis and moderate perisplenitis.

COMMENT

In Case 1 thrombosis of the splenic vein was definitely seen at the time of operation; in Case 2, while no thrombi were seen in the vein, the vein appeared fibrotic and sclerotic and was completely occluded. The adhesions and severe bleeding encountered in Case 2 are not unusual since a collateral circulation at various points is not infrequently established in this condition. In this case a collateral circulation involving the diaphragm and lateral peritoneum was present. In view of the fact that a collateral circulation is established at many points, the wisdom of merely tying off the splenic vein and artery, as was done in Case 1, may be questioned. In both cases a definite leucopenia was present and persisted even after splenectomy. Only Case 2, however, had a thrombopenia.

As has already been mentioned, most observers regard leucopenia as a more or less constant finding in this disease. Smith and his coworkers,[1] however, are of the opinion that leucopenia is not a characteristic feature of chronic thrombosis of the splenic vein. Diamond[5] also states that the blood shows no anemia, leucopenia, or thrombocytopenia, and he employs this fact as a means of differentiating chronic thrombosis of the splenic vein from splenic anemia or "leucopenic splenomegaly," as he terms it. In addition, he considers the presence of unalterable splenomegaly as characteristic of splenic anemia. We cannot agree with this view since both our patients had a definite and constant leucopenia, and yet the spleen decreased in size immediately after a gastric hemorrhage and became large again two or three days after bleeding had stopped. In addition, in Case 2 there was a very definite although of course temporary reduction in the size of the spleen after the injection of five minims of adrenalin. In only Case 2 did a marked increase in the number of platelets occur after operation. A great increase in the number of platelets occasionally occurs after splenectomy and may result in venous thrombosis in other parts of the body with the production of serious and alarming symptoms.

In Case 1 bleeding continued after ligation of the splenic vein and artery; thus three severe gastric hemorrhages occurred after the operation, one in 1935 and two in 1937. Whether these hemorrhages could have been prevented had the spleen been removed is problematic; we do feel, however, that splenectomy, omentopexy, and coronary vein ligation offer a better outlook as far as the prevention of subsequent bleeding is concerned. In this case liver function tests, done at the time of the third admission to the hospital, gave definite evidence of liver damage. In Case 2, advanced cirrhotic changes were present at the time of operation; yet liver function tests done immediately before operation gave no evidence of liver damage.

DISCUSSION

A detailed discussion of the etiology, symptomatology, and treatment of this disease will not be given since it is beyond the purpose of this communication. These phases of the subject have been ably presented by Smith and his co-workers, Wallgren, van Creveld, and Nobel and Wagner.[1] So, too, it is not our desire to enter into a discussion of the question of whether this condition is an early phase of Banti's disease, as Warthin[6] believes, or whether it is a distinct entity. It is our purpose, however, to stress the importance of early recognition before gastric bleeding occurs. A striking feature in both our cases was the severe gastric hemorrhage which occurred as the first warning of the disease; indeed, this is the mode of onset in the majority of cases. The hemorrhage is usually severe and alarming and one to two large transfusions may be required to combat the subsequent severe anemia. As a rule, unless proper treatment is instituted and, at times, even after splenectomy, later hemorrhages may occur and produce a fatal outcome; cases have been reported in which death occurred even with the first hemorrhage. Immediately after the hemorrhage none or only slight enlargement of the spleen is present; after the bleeding has stopped, the spleen becomes enlarged and can be felt three to four fingerbreadths below the costal margin. Enlargement may be accelerated if transfusions are given as occurred in both our cases. With each recurrence of the bleeding the spleen diminishes in size only to enlarge again after the patient has recovered from the blood loss. Hematemesis is a dangerous symptom and was the cause of death in all of the fatal cases except two reported by Smith and Farber. We propose, therefore, that an effort should be made to recognize this disease before the occurrence of hematemesis. It is believed by many authors[7] that removal of the spleen relieves a great deal of the strain on the esophageal and gastric varices and thus prevents the occurrence of gastric bleeding.

It is our opinion that the roentgenologic demonstration of esophageal varices is a diagnostic feature which should be given careful consideration. We believe that the best single sign for the early recognition of this disease is the visualization of varices in an esophagram. Varices should be looked for roentgenologically in every patient who has an unexplained splenomegaly. The presence of esophageal varices in a patient with an enlarged spleen which cannot be explained satisfactorily, even without gastric hemorrhage, is sufficient indication for splenectomy and coronary vein ligation. Indeed, it is highly desirable to operate before gastric hemorrhage occurs. Ligation of the coronary vein, in addition to splenectomy, is recommended because splenectomy alone is not always effective in preventing later bleeding. Several authors[1] have observed hematemesis one to ten

years after operation when splenectomy alone was done. McIndoe[8] also considers ligation of the coronary vein in addition to splenectomy a valuable method of treatment for the prevention of later hemorrhage. An interesting observation was made by Smith and Farber in one of their patients in whom ligation of the veins of the gastrohepatic omentum, from the cardiac to the pyloric end of the stomach, was done one year after splenectomy. One month later the dilated esophageal veins, observed by esophagoscopy, were definitely smaller than before the ligation. We believe, however, that esophagoscopy is dangerous in these cases and that adequate information can be obtained from the esophagram; in addition, demonstration of esophageal varices by roentgen-ray examination is more reliable. Unfortunately, ligation of the coronary vein was not done in our second patient because her condition was considered too poor at the completion of the splenectomy to permit any further operative procedures. We expect, however, to make several roentgenologic studies of her esophagus after she has recovered from the splenectomy and, if the varices appear as prominent and as numerous as before, we will recommend reoperation for the purpose of ligating the coronary veins.

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THE ANEMIA OF RHEUMATIC FEVER

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IT IS a matter of common clinical observation that anemia may accompany the active phases of rheumatic fever. We have been interested in studying the development of this anemia and in determining, if possible, what factors might be involved in producing it.

Infection has been well established as one of the commonest causes of secondary anemia. It is generally described as either destroying the erythrocytes, giving a hemolytic type of anemia, or suppressing erythropoiesis, resulting in a hypoplastic anemia. The hemolytic factor appears in septicemia due to the *Streptococcus hemolyticus*[1] or *B. coli*, to puerperal sepsis, or infections with *B. welchii*,[2] or to malaria.[3] Anemias from decreased blood formation are likely to result from chronic infections. Blackfan, Baty, and Diamond[4] have presented one case of severe anemia secondary to an abscessed tooth and another associated with tonsillitis, cervical adenitis, and otitis media. Douglas and Tannenbaum[5] and Kugelmass and Lampe[6] also present evidence favoring the view that chronic infections retard erythropoiesis. This hypoplastic type of secondary anemia is characterized as microcytic or hypochromic, according to Wintrobe's classification.[7] Typically, there is no elevation of circulating reticulocytes, or of icteric index,[8] and no evidence of increased bilirubin in the blood. Usually there is a return to normal blood levels as the infection subsides.[8]

Douglas and Tannenbaum,[5] from observing normal levels for the icteric index and reticulocytes, have attributed the anemia of rheumatic fever to this latter factor of diminished blood formation. Castle and Minot[1] also state that this type of anemia may develop rapidly in rheumatic fever. On the other hand, Kapp and Coburn[9] indicate that blood destruction is the important factor. We have been impressed by the rather rapid development of anemia which is often quite severe, and have therefore attempted to clarify this problem by careful study of selected groups of rheumatic fever patients during prolonged hospitalization.

METHODS

The study has been planned to observe the changes in the blood associated with the characteristic recrudescences of rheumatic fever activ-

From the House of the Good Samaritan, Boston, Massachusetts, and Irvington House, Irvington-on-Hudson, New York.
The expenses of this study have been defrayed by a grant from The Commonwealth Fund.

ity. A combined group of patients, in part from the House of the Good Samaritan (Boston) and in part from the Irvington House (New York), was therefore selected, and the blood levels followed during the period of hospitalization. Any group of convalescent rheumatic fever patients may, during the normal course of events, develop exacerbations of the disease. In our combined group a considerable number of exacerbations did occur, and we were therefore able to study the blood picture before, during, and after the recrudescence. From basal levels established before the episodes of renewed activity, we were able to observe the changes in the blood picture resulting from the active phase of the disease.

There were in all seventeen patients who had a total of nineteen recrudescences, two patients having two recrudescences each. All had well-established rheumatic fever with cardiac complications. They ranged in age from 5 to 16 years. None received any drugs which could be considered to have any bearing on the production of anemia. The patients were treated with the usual supportive measures including salicylates, diuretics, and digitalis. Six of the exacerbations progressed to a fatal termination. All other patients were followed during their convalescence until the activity subsided.

In order to obtain as uniform values as possible, blood samples have been taken whenever possible at the same time of day, avoiding diurnal fluctuations. The sedimentation rates at the House of the Good Samaritan were done by the method of Rourke and Ernestene.[10] Those at Irvington House were done in Linzenmeier tubes, read at the end of one hour only, and not corrected for anemia. The icteric index was obtained by comparison with a Helige color standard. The serum bilirubin was determined by the usual quantitative van den Bergh reaction. Urobilinogen values were obtained from single fresh specimens of urine by applying the Erhlich aldehyde reaction to dilutions of urine ranging from 1:20 to 1:160 or higher if necessary.

The criteria which we have required in order to establish a recrudescence have included clinical and laboratory observations. In all of the episodes listed in Table I, there has been a distinct change in the clinical course of the patient indicative of renewed or increased activity of the disease such as pyrexia, tachycardia, epistaxis, anorexia, nausea, and often joint pains and evidence of increased cardiac damage and failure. The sedimentation rate has been elevated well above normal in every instance except one (No. 8). Here the low rate may be attributed to the coincident cardiac failure—an observation first made by Westergren[11] and one which we have frequently confirmed. The total leucocyte count and Schilling index have been elevated in every case.

RESULTS

In Table I is presented a summary of the determinations significant in the study of the anemia which was found to develop in every one of

TABLE

LABORATORY DETERMINATIONS BEFORE, DURING,

RECRUDESCENCE NO.	HOSPITAL NO.	NAME	SEX	AGE	RED BLOOD CELLS (MILLIONS)			HEMOGLOBIN (%)			HEMATOCRIT		
					BEFORE	DURING	AFTER	BEFORE	DURING	AFTER	BEFORE	DURING	AFTER
1	HGS 6245	R. A.	F	6	4.3	4.0	4.3	78	70	77	35	35	35
2	HGS 6245	R. A.	F	6	4.3	3.9	4.4	76	70	78	35	34	38
3	HGS 6305	L. B.	F	16	4.9	4.1	4.7	80	72	82	41	34	40
4	HGS 6107	E. C.	F	9	4.5	3.7	--	77	60	--	39	30	--
5	HGS 6340	G. D.	M	11	3.6	2.6	--	58	35	--	26	20	--
6	HGS 6293	E. F.	F	14	4.8	4.4	--	80	75	--	38	38	--
7	HGS 6271	W. F.	M	5	4.9	3.4	--	81	53	--	40	27	--
8	HGS 6278	E. G.	M	6	3.7	3.0	--	50	40	--	29	26	--
9	HGS 6111	W. L.	M	11	4.5	3.0	--	69	51	--	36	32	--
10	HGS 6297	R. L.	F	10	5.1	4.0	5.0	83	63	78	41	30	38
11	HGS 6297	R. L.	F	10	5.1	3.9	4.9	78	64	84	40	31	38
12	HGS 6281	F. L.	M	10	--	4.4	5.6	--	75	87	42	35	42
13	HGS 6286	M. M.	F	6	--	3.8	4.5	--	68	78	40	29	41
14	HGS 6407	A. S.	M	11	--	3.1	5.1	--	60	82	--	26	39
15	IH 3254	I. I.	M	11	4.7	3.9	5.8	90	79	95	--	--	--
16	IH 3281	H. R.	F	8	4.4	2.7	4.0	83	61	78	--	--	--
17	IH 3239	H. Z.	M	14	6.0	3.4	--	100	71	--	--	--	--
18	IH 3249	A. D.	F	9	4.5	3.3	4.8	91	78	90	--	--	--
19	IH 3120	D. B.	F	10	4.7	3.8	4.5	91	77	91	--	--	--

the recrudescences. The columns giving comparisons of the levels of the number of red blood cells, the hemoglobin, and hematocrit before, during, and following the increased activity show invariably a distinct drop in all three. The resulting anemia is often quite severe (see No. 5 and 16) and would seem to constitute a further source of embarrassment to the already damaged heart. As the infection subsides, the blood levels tend to rise without any specific therapy and may soon reach their former values.

Determinations have also been made of the color index, the mean corpuscular volume, the mean corpuscular hemoglobin, and the mean corpuscular hemoglobin concentration before, during, and after the recurrence. These have not been included in the table since they contribute very little. The color index, low at first, remains low indicating a moderate degree of hypochromia. The cell size, the mean corpuscular hemoglobin, and hemoglobin concentration vary irregularly from low to normal values.

To determine whether, in the production of the anemia, we were dealing primarily with a hypoplastic or hemolytic factor, we measured also the icteric index, the serum bilirubin, the urobilinogen excretion, and reticulocyte level in all phases of the disease. The icteric index and the quantitative van den Bergh tests were found to contribute little. There were 100 determinations made by the indirect quantitative van den

I

AND AFTER RECRUDESCENCES OF RHEUMATIC FEVER

RETICULOCYTES (PER 1000 RBC)			UROBILINOGEN			REMARKS
BEFORE	DURING	AFTER	BEFORE	DURING	AFTER	
2.0	2.4	1.0	--	40	--	Recrudescence 3 weeks following a cold
.8	4.5	.4	30	80	<20	Recrudescence 2 weeks following positive hemolytic streptococcus throat culture
1.2	1.0	1.0	<20	40	<20	Recrudescence 4 weeks following sore throat
1.2	4.8	--	<20	80	--	Renewed activity initiated by discontinuing aspirin
1.0	6.5	--	--	320	--	Recrudescence leading to death
0.8	2.3	--	30	160	--	Recrudescence leading to death
--	5.3	--	--	160	--	Recrudescence leading to death
3.4	4.7	--	<20	160	--	Recrudescence leading to death
2.0	6.0	--	40	320	--	Fatal recrudescence 2 weeks after a sore throat
2.8	6.2	0.6	30	320	<20	No preceding respiratory infection
1.4	6.5	1.5	30	160	<20	No preceding respiratory infection
--	5.4	2.3	--	40	<20	Mild recrudescence precipitated by a respiratory infection
--	2.5	0.7	--	40	<20	Mild recrudescence precipitated by a respiratory infection
--	4.5	0.3	--	80	<20	No preceding respiratory infection
1.0	4.0	2.0	--	20	<20	Mild recrudescence precipitated by a respiratory infection
.3	4.0	--	--	--	--	No preceding respiratory infection
.5	3.0	--	--	60	--	Recrudescence leading to death precipitated by extraction of abscessed tooth
1.0	4.0	--	--	20	<20	No preceding respiratory infection
.3	4.0	1.0	--	<20	<20	Mild recrudescence precipitated by a respiratory infection

Bergh method, and 428 readings of the icteric index. A considerable number of patients showed slight increases over the normal in both these tests. Considering five the upper limit of normal for the icteric index, there were 249 out of 428 determinations (58 per cent) which were greater than normal, but none were above 15, which is the level at which visible jaundice develops. Similarly, from the quantitative van den Bergh test there is indication of slightly increased levels of serum bilirubin. Considering 1.0 mg. of bilirubin per cubic centimeter of serum a generous upper limit of normal,[12, 13] there were 68 of 100 determinations which were slightly or moderately elevated. However, as shown in Table II, there was no apparent correlation between the degree of activity of the disease and the amount of serum bilirubin. Further-

TABLE II

ICTERIC INDEX AND SERUM BILIRUBIN VALUES RELATED TO ACTIVITY OF RHEUMATIC FEVER

ACTIVITY OF DISEASE	ICTERIC INDEX			SERUM BILIRUBIN		
	NUMBER OF DETERMINATIONS	RANGE OF VALUES	AVERAGE	NUMBER OF DETERMINATIONS	RANGE OF VALUES	AVERAGE
Inactive	178	2-11	6.6	18	0.3-4.1	1.6
Mild activity	204	2-15	6.8	51	0.4-5.0	1.7
Severe activity	46	1.5-14	7.2	31	0.4-3.0	1.5
	428	1.5-15	6.7	100	0.3-5.0	1.6

more, when consecutive estimations were made during the course of a typical recurrence, the readings varied with no consistency.

Determinations of urobilinogen were also included in the study. The method of Wallace and Diamond[14] was used. According to these au-

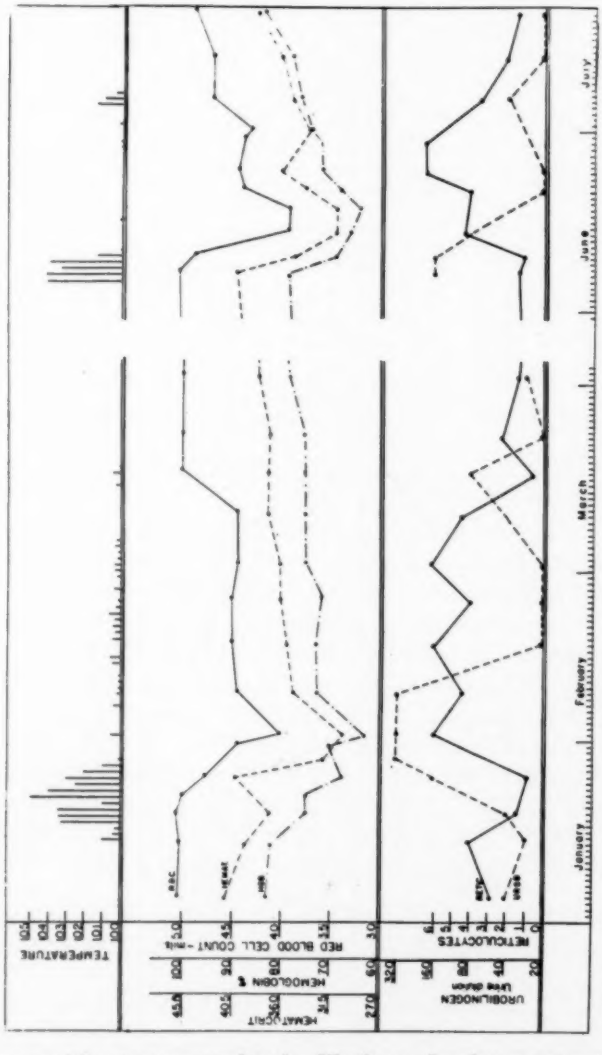

Chart 1.—Two spontaneous recrudescences of rheumatic fever in patient R. L., HGS No. 6297. Recrudescences characterized by fever and cardiac insufficiency.

thors, a positive test appearing in dilutions of urine greater than 1 to 20 may be considered as indicating an abnormal amount of urobilinogen, and the greater the dilution in which the test is positive, the larger the amount of urobilinogen in the urine. Single fresh specimens have been

analyzed rather than twenty-four-hour amounts in order to avoid any deterioration of urobilinogen on standing. Obviously this does not give any estimations of absolute amounts; it does, however, give an indication of the extent to which abnormal quantities are excreted, and, when its limitations are kept in mind, it has proved a useful test.[15, 16] In Table I and also in Charts 1, 2, and 3 the values are given as the greatest dilution of urine in which a positive test may be detected. Our observations support those of Wallace and Diamond in that a 1:20 dilution of urine appears to be the greatest in which a positive test appears in normal individuals.

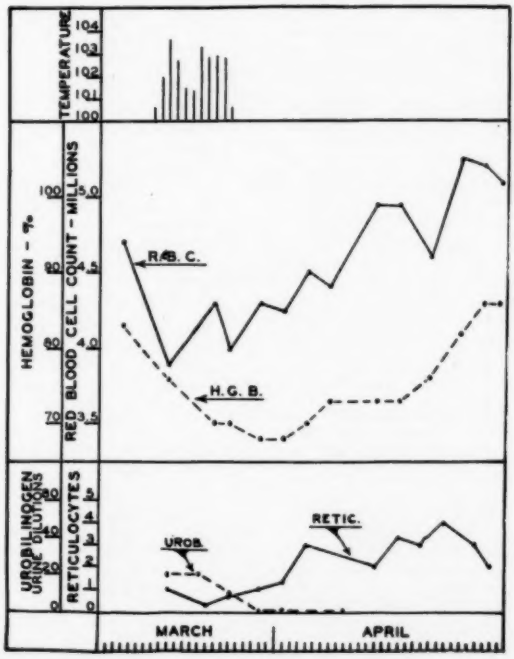

Chart 2.—Recrudescence of rheumatic fever precipitated by a respiratory infection in patient I. I., IH No. 3254. Recrudescence characterized by joint pains and increased valvular damage.

As indicated in Table I, the severe recrudescences have been associated with abnormal urobilinogen excretion and the less severe or milder ones with little or no increase over the normal. In those instances in which the higher values occurred, there was also passive congestion with which there may have been concurrent liver damage. It is difficult to know, therefore, whether the abnormal excretion was due, at least in part, to increased blood destruction, or whether entirely to liver damage, for it is well established that both factors may be associated with excess urobilinogen in the urine.[17] The same may be said of the

finding of increased excretion of coproporphyrin reported by Kapp and Coburn.[9] Unless the factor of liver damage is excluded, it would seem inconclusive to attribute coproporphyrin in the urine to hemolysis.

Reticulocyte counts have been included as an index of bone marrow activity.[18] In all of the recrudescences there was observed a slight but significant increase which appeared to follow shortly after the period of greatest disease activity. It occurred sometimes during the gradual subsiding of the recrudescence while low-grade fever and increased sedimentation rate, etc., continued, or when the disease process appeared

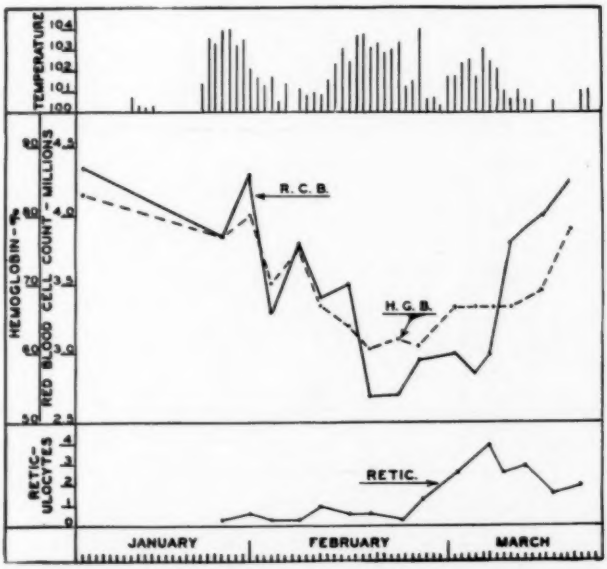

Chart 3.—Spontaneous recrudescence of rheumatic fever in patient H. R., IH No. 3281. Recrudescence characterized by polyarthritis, appearance of rheumatic nodules, and prolongation of P-R interval.

quiescent. This would seem to indicate that we are dealing with a suppression of erythropoiesis during the height of disease activity and that when this suppression is withdrawn there follows increased red blood cell formation as indicated by the increase in circulating reticulocytes. Whether or not this is the sole factor, or whether hemolysis may also occur, we cannot be sure. The rapidity with which the anemia sometimes develops suggests that actual destruction of red cells may also be taking place. In any event, however one explains the cause of the anemia, the important fact is that there develops with rheumatic fever a secondary anemia which is often quite severe. As infection subsides, the blood tends to return spontaneously to the original level. The presence of the anemia may therefore often be an indication of disease activ-

ity and should be added to other criteria such as increase in sedimentation rate and leucocytosis as helpful aids in determining when the disease may be considered quiescent.

SUMMARY

Prolonged observation of patients hospitalized for rheumatic fever has permitted a study of the blood changes associated with characteristic recrudescences of the disease. In association with the active phases of the disease, there develops a secondary anemia which is often quite severe. As the infection subsides, the blood levels tend to return to normal. Therefore, the presence of anemia may often be an indication of continued rheumatic fever activity.

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ACRODYNIA TREATED WITH INTRAMUSCULAR INJECTIONS OF VITAMIN B_1

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IN THE twenty years since Dr. Bilderback reported the first cases of the disease now known as acrodynia, no specific or effective therapy has been discovered. Dr. Bilderback concludes his monograph in Brennemann's *Practice of Pediatrics* with the following statement: "The physician who treats a patient with acrodynia from every angle and

Fig. 1.

Fig. 2.

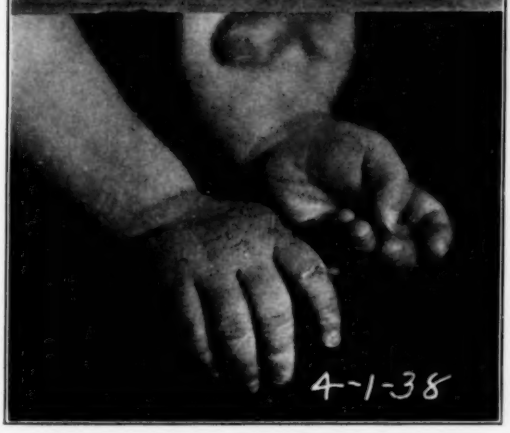
does everything that has been advocated will stand by the bedside of a child suffering from acrodynia and feel that in this instance he is still a therapeutic pauper. It is well to tell the parents at the very beginning that the disease is chronic and that it will be many weeks, or even months, before the child will get better."

Two cases of this disease which recently came under our observation were given injections of vitamin B_1 with strikingly good results. We are reporting them in the hope that our findings will be confirmed by other clinicians.

CASE 1.—(Figs. 1-4.) The patient, J. R., a 14-month-old girl, was first seen by us March 13, 1938. About two months earlier, she had developed a generalized, scaly, red, pruritic eruption of the skin. Coincident with the appearance of the

Fig. 3.

Fig. 4.



rash she had become listless, apathetic, and weak, with occasional slight afternoon fever and marked loss of appetite. It was noted that she had lost her normal cheery disposition and had become irritable and depressed with the illness.

The rash over the trunk had cleared rather promptly, but the hands and feet continued red and beefy and itched severely. A variety of local treatments had failed to alter these lesions, and, because she continued to lose weight and strength, she was brought into the Children's Orthopedic Hospital.

Further history revealed that the patient was youngest of three children of healthy, white American farmer parents. Prenatal, birth, and antenatal history was not remarkable. She had been breast fed for several months and then was fed a soft baby diet apparently adequate for the needs of the average child of

her age. Developmental history was normal, and her history was entirely negative for illness except for an occasional common cold. The two older siblings were in excellent health. The parents knew of no similar cases in the area in which they lived; in fact, the physicians in the area had not established a diagnosis in this case, not having seen the illness before.

Examination showed the infant to be fairly well nourished and appearing acutely ill, listless, and atonic. She cried as soon as anyone approached her and rubbed and scratched her hands and feet constantly. There was moderate photophobia, and the child was unable to sit or stand alone. The nose and cheeks were red; the hands and feet moist, cool, scaling, slightly edematous, deep red in color, with superficial infection around the nails of the fingers and toes, these being most involved in the process. The skin of the trunk showed a fading rash with fine desquamation. There were coryza and bronchitis with a small area of pneumonia in the right upper lobe which was demonstrated by x-ray. The mouth was red and inflamed and the inside of the lips and adjacent gums were covered with superficial ulcers measuring 0.5 to 1 cm. in diameter. Two of the incisor teeth were loose. There was a moderate degree of generalized lymph node enlargement. Aside from marked general muscular atony and absent deep tendon reflexes, the remaining physical findings were negative.

Laboratory study showed a hemoglobin of 13.0 gm.; 4,660,000 erythrocytes; 8,000 leucocytes, with 60 per cent polynuclear cells and no pathologic cells seen. Blood Wassermann and Kahn tests were negative, and the urine was negative except for a trace of albumin and a trace of acetone. A blood pressure reading taken March 20 was 108 systolic, 66 diastolic.

During her first three days in the hospital the temperature gradually climbed to 103.4° F. rectally. She was given supportive care, oral hygiene, moist compresses to the infected extremities, and treatment was directed against the pneumonia. On the fourth day the temperature dropped, and the respiratory infection appeared to be clearing. The involvement of the mouth, hands and feet, the general muscular atony, and the depression were improved.

Since the few pathologic studies of acrodynia show involvement of nervous tissue and since many features of this case suggested involvement of the peripheral, sympathetic and central nervous systems, we decided, more or less empirically, to give massive doses of crystalline vitamin B_1 hypodermically.

On March 16 daily intramuscular injections of crysto-vibex, 2000 units, were begun and continued for six days. On March 19, we noted a marked improvement in the patient's general condition. The skin lesions were definitely improved, muscle tone noticeably better, appetite improved, and the child was more alert and cheery.

At general pediatric rounds March 24 the following notation was made: "This child has made a remarkable improvement since beginning vitamin B therapy. The mouth lesions have entirely cleared and the loose teeth are now firm. The child is sitting up in bed, eating fairly well; infection and itching of hands and feet have disappeared. Restraints were removed three days ago. Fingers and toes still definitely pink. Nurses note that perspiration is markedly reduced."

We had discontinued parenteral vitamin B on March 21, three days prior to above note, and had substituted a 600 unit tablet daily by mouth. On March 25, four days later, the rapid improvement seemed to cease, and there was a rather marked exacerbation of the symptoms. On March 28 the child was again more lethargic; there were increased redness, scaliness and itching of the hands and feet; and the marked muscle weakness returned.

Since the child had become worse in spite of oral vitamin B administration, injections of 2,000 units every second day were again instituted, and six more doses were given. Improvement began at once. The child gained 1¼ pounds in weight, resumed play, and began to stand in her crib. Photophobia disappeared.

Only occasional pinkness of hands and feet was observed. Because of a mild upper respiratory infection, the child was kept in the hospital until May, and a third series of injections was given. Blood pressure taken on May 16 was 90 systolic. There were few, if any, signs of acrodynia after April 21. The child gained in all 3¾ pounds in weight.

CASE 2.—(Referred by Dr. Frank Miller, of Everett, Wash. First examined March 16.) M. H., a 20-month-old girl weighing 23¾ pounds, whose symptoms began three weeks previously with irritability, loss of appetite and weakness, presented the classical picture of misery and discomfort; she had ceased to walk and play, desired to be held all the time, and whined and cried a great deal. She rubbed her eyes, even putting her fingers between the lids and rubbing the eyeballs. Her mother stated that she had her fingers in her mouth a great deal of the time.

Examination showed the child to be not badly nourished, but atonic. She hung her head and avoided the light. The hands and feet were cold, bright red, and scaling about the fingers and toes. The mouth was red, but no marked ulcers or loose teeth were noted at time of initial examination, although six days later she developed a moderately severe stomatitis. The systolic blood pressure was 110. In short, she gave a typical picture of uncomplicated acrodynia.

Because of the definite improvement shown in the first patient during the treatment with vitamin B, when given hypodermically, I wrote Dr. Miller and asked him to begin the injections. On March 22 he gave the first of six daily injections of betalin S, 2,000 units each.

He sent me a letter April 1, giving the following report:

"*March 23:* Less irritability; appetite better; less photophobia.

"*March 24:* Marked improvement in photophobia and irritability; less redness of extremities. Patient has developed a mild coryza which hinders her breathing somewhat.

"*March 26:* No change in condition from yesterday.

"*March 27:* Appetite improved (relishes vegetables); hands greatly improved but less improvement in feet. Eyes better, but mouth still very sore; legs unsteady and child feels better lying down.

"*March 31:* Hands seem virtually normal in color and are warm; still some redness of feet and still cold; appetite good; bowels not good; photophobia better, but bright light still bothers her some; legs improved, does some walking now with as much steadiness as normal; still suffering from an acute coryza. Her general condition seemingly improved and satisfactory. (Patient now receiving daily oral vitamin B.)"

The child was again examined by us on April 15. Her weight was unchanged, and the blood pressure was 105 systolic. There had been no improvement, but rather a decided increase in the symptoms since the intramuscular injections were discontinued. There was an ulcer 1 cm. in diameter on the side of the tongue. Gums were swollen, and the lower left central incisor was loose. The roof of the mouth was red and corrugated. The hands and feet were somewhat pink. Child could walk but wanted to be held and to have extremities rubbed. The eyes were inflamed.

The family moved to Kirkland, Wash., at this time, and Dr. E. C. McKibben again resumed the parenteral vitamin B_1 at two- to three-day intervals. On April 30 the child was again brought in. The mother stated that the child had seemed "about normal" until she contracted a cold two days previously. Slight redness of fingers and toes was noted. Mouth had healed, tooth was very slightly loose. Mother stated that child rubbed her eyes only when sleepy. A few days later the father reported to us that the child had completely recovered.

COMMENT

The two cases of acrodynia described showed dramatic improvement within three days after beginning intramuscular injections of vitamin B_1. In both cases the improvement ceased and the symptoms grew worse when these injections were discontinued, and the vitamin was given by mouth. Because it has been reported that vitamin B was not absorbed in cases of achlorhydria, a gastric analysis was done in the first case and both free and combined hydrochloric acid were found present in fair amount. The first case was also given nicotinic acid for a period of two weeks, but it was after marked improvement had been made, and we could not see that it hastened the recovery. In spite of the relapses which occurred when treatment by mouth was tried, both cases had recovered in six weeks from the beginning of injection treatment. We believe that this period might have been greatly shortened had the intramuscular administration been given continuously at two- to three-day intervals.

IDIOPATHIC DILATATION OF THE COMMON BILE DUCT IN CHILDHOOD

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IN MODERN medical practice there are, fortunately, but few conditions which carry a diagnostic error of 98 per cent. When such a situation prevails it is the result of the fact that the signs and symptoms of the condition are vague and ill defined or the literature is so sparse that very few physicians have had the opportunity of becoming sufficiently familiar with the signs and symptoms to enable them to arrive at a correct diagnosis.

Idiopathic dilatation of the common bile duct falls into the latter classification. Gross[1] recently reviewed the literature and found records of ninety-eight cases to which he added two of his own, bringing the total so far reported to 100. The case here reported brings the total to 101. Fifty-three have occurred in childhood or presented symptoms present from childhood to adult life.

Of these fifty-three cases only three have been correctly diagnosed preoperatively. Were the symptoms and signs of the condition vague, bizarre, or widely variable in character such a high percentage of failure might be expected and might be expected to continue. Actually, however, they are definite, clearly cut, and concise. Future failures could only be due, as was ours, to the lack of proper publicity of the syndrome. With this in mind and with the knowledge that a correct preoperative diagnosis greatly enhances the patient's chances of recovery, it is deemed proper to report another case and to review again the outstanding features of this striking anomaly.

CASE REPORT

M. S., a Mexican girl, aged 10 years, was admitted to the Children's Hospital March 9, 1932.

Family History.—The father and mother were living. The mother was said to have had active tuberculosis six years ago. Siblings, aged 11, 9, 8 and 6 years, were all living and well.

Complaints.—(1) Pain in the right side just below the ribs; periodic for five years. (2) Constant pain in this region for the past two weeks. (3) A mass, the same size for five years, present below the ribs.

For the past five years the child had periodic attacks of pain in the right upper abdomen. Coincident with the onset of pain a mass appeared at the costal margin on the right side. The child said this mass was painful. Associated with the pain was listlessness, nausea, and refusal of food. If food was taken, during the attack, it was always vomited.

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The duration of an attack was variable, being on occasions as short as twenty-four hours but at other times as long as two or three days. The onset was usually sudden and recovery rapid. During the past two weeks she had been in almost constant pain, with only occasional short periods of relief. Between attacks she felt well, was very active and attended school.

Physical examination revealed a well-developed and well-nourished child who did not appear acutely ill; height 50½ inches, weight 57 pounds. There was a definite but slight icterus of the sclerae but none noted of the skin. The remainder of the physical examination was normal or irrelevant except for the findings in the abdomen.

Abdomen.—The abdomen, generally, appeared flat. The respiratory waves were even and normal in excursion. Palpation, in the recumbent position, revealed no rigidity or tenderness. The liver edge was felt along the right costal margin. Just to the right of the midline a mass, about the size of an egg, was felt. This mass felt cystic and could be definitely separated from the liver edge. On inspiration the mass moved away from the rib margin and on expiration toward it. Percussion over the mass revealed a tympanitic note over its distal portion. At times a mass, similar in size and shape, was felt at the same level just to the left of the midline. This seemed to be a partially filled stomach. On palpating the abdomen during auscultation over the mass one heard a splashing sound. In the erect position the mass was distinctly visible and was seen to go up and down with respiration.

The following possibilities were considered: (1) gall bladder disease; (2) extra or anomalous lobe of the liver causing pressure on the common bile duct; (3) echinococcus cyst; (4) simple liver cyst; (5) tumor of the kidney or of the adrenal gland.

Laboratory procedures and findings.—Tuberculin O. T.: 1.0 mg. positive in 48 hours. Blood: Wassermann and Kahn tests negative; hemoglobin 78 per cent, red blood cells 4,010,000, white blood cells 6,800, polymorphonuclears 46 per cent, lymphocytes 50 per cent, monocytes 2 per cent, eosinophiles 2 per cent. Fragility test: Hemolysis begins at 0.38 per cent and ends at 0.28 per cent. Control begins at 0.38 per cent and ends at 0.28 per cent. Echinococcus complement fixation negative. Van den Bergh: (1) Direct reaction: color began to develop in five seconds and had reached its maximum in two minutes. Prompt or immediate reaction. (2) Indirect reaction: bilirubin 3.5 units or 17.5 mg. per liter of serum.

Urinalysis: Occasional white blood cells were found on two occasions. Traces of bile were present on four occasions. Urine culture produced *B. pyocyaneus.* No typhoid bacilli were found. Stool Examination: Clay colored; bile test negative. Blood was present by the benzidine test. Microscopic examination showed the presence of a few red blood cells but no ova or parasites were found. Many fat globules were present. Culture revealed *B. coli communis* but no pathogenic organisms. Total fat 321 mg. per gram of dried feces, 32.1 per cent. Fatty acids 235.8 mg. per gram of dried feces—73.5 per cent of total fat. Neutral fat 85.2 mg. per gram of dried feces, 26.5 per cent of total fat.

Cystoscopic examination was negative.

Roentgenograms of the chest and the gastrointestinal tract were negative. The kidney shadows were outlined without demonstrable abnormality. A rounded, soft tissue shadow seen below the border of the right kidney was found to be distinct from the kidney. The gall bladder was not outlined by roentgenograms after two attempts with oral administration of the dye.

During the period of observation the mass in the right upper abdominal quadrant was constantly present though it varied in size from time to time. The icterus of

the sclerae remained constant. The stools remained constantly acholic. An attempt to aspirate the duodenum by means of Rhefus tube failed because the tip did not pass through the pyloris.

It was felt that echinococcus disease and tumor of the kidney or adrenal gland had been satisfactorily ruled out. It was also felt that tuberculosis was not the cause of the condition in spite of a positive tuberculin test.

Although no definite diagnosis was made, the child was referred to the surgical service because of the continued biliary obstruction associated with a tumor mass.

Operation was performed April 6, 1932, by Dr. J. Norton Nichols.

After proper exposure the tumor mass was found to be a large cyst, the size of a man's wrist, of the common duct. There were adhesions between the cyst and the surrounding structures—gall bladder, liver, and duodenum. Above, the cyst could be traced to the under surface of the liver and distally behind the duodenum to the ampulla.

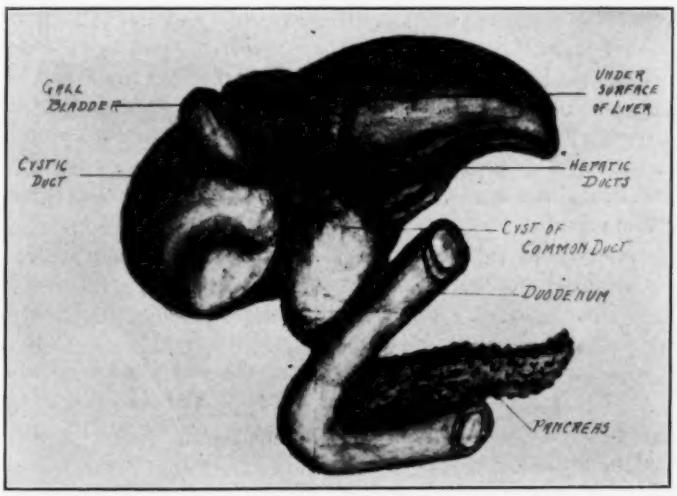

Fig. 1.—A semidiagrammatic drawing illustrating the size of the cyst of the common duct and its relation to adjacent organs.

The gall bladder was slightly larger than normal and had markedly thickened walls. Pressure on the cyst produced an enlargement of the gall bladder, demonstrating the potency of the cystic duct.

The liver was enlarged and extended considerably below the costal margin.

The gall bladder was aspirated and 240 c.c. of black bile removed. This procedure collapsed the cyst to a marked degree. It was felt that an anastomosis between the gall bladder and the gastrointestinal tract was the only surgical solution of the problem. Because of the fixed positions of the structures involved by firm adhesions, the only possible anastomosis was between the gall bladder and the duodenum. While these structures were open an effort was made to pass a probe through the cyst into the duodenum, but the attempt failed. Patency of the lower end of the cyst, though suspected from the history, could not be proved.

A cholecystduodenostomy was accomplished without incident, and the child made an uneventful recovery.

On Sept. 15, 1932, she was readmitted for observation. She had been perfectly well since leaving the hospital and had gained 7 pounds in weight. There had been

no jaundice, pain, or distress. Physical examination revealed no abdominal mass. The liver edge could not be felt nor could the tip of the spleen. The van den Bergh test showed a delayed or negative reaction, no color developing after forty minutes. The indirect reaction showed 9.2 units or 4.6 mg. per liter of serum. Hydrobilirubin was present in the stool, but other bile pigments were absent. The icteric index was 7. The blood count was normal.

Another admission in 1936 again revealed a well girl, normally developed for her age and with no symptoms referable to the condition.

This case presents another instance of this remarkable condition. The history and findings are typical for the entire group. Although the percentage of diagnostic error has not been lowered, the list of operative cures has been increased by one.

To avoid future diagnostic failures it is only necessary to remember the triad:[1] abdominal pain (65 per cent); (2) jaundice (85 per cent); abdominal tumor (90 per cent). These symptoms and signs occurring in a child should point to a cyst of the common bile duct as a major possibility. Should the child be a female the condition becomes a major probability, it having been pointed out by Gross that females are involved three times as frequently as males. For a more detailed discussion of the signs, symptoms, and differential diagnosis, the reader is referred to the article by Gross.

The etiology of this condition remains unknown. As pointed out by Gross, no one of the theories so far presented is applicable to all of the cases reported. When such a situation prevails, it becomes highly probable that the causes are varied and multiple. In the case here presented a valvelike obstruction at the ampulla seems probable because of the continued variations noted in the size of the tumor. However, it was not possible to demonstrate such a condition at the time of operation.

It is now rather well established that when it is desired to drain the gall bladder into the gastrointestinal tract that a cholecystgastrostomy is the operation of choice because of the reduced opportunity for ascending infection. In this instance such an operation was impossible, and the anastomosis to the duodenum was successful. Twelve patients have now been operated upon in this manner, and eleven have been successful.

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THE SERUM TREATMENT OF MENINGOCOCCIC MENINGITIS

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CONSIDERABLE interest in the problem of meningococcic infections has been stimulated recently by the development of new methods of treatment. The demonstration by Ferry[1] in 1931 of a meningococcus exotoxin and the therapeutic use of an antitoxin by Hoyne,[2] Fisk,[3] Lindsey and others[4] gave rise to a number of interesting questions. The introduction of sulfanilamide also promises to bring a valuable addition to our therapeutic resources. The use of antitoxin brings up several problems, the chief of which are (1) the question of the superiority of antitoxin over antibacterial serum and (2) the advisability of supplanting intraspinal methods of treatment in meningitis by intravenous injections alone. Hoyne[5] has recently abandoned the intraspinal route in therapy and states that in most cases the exclusive use of intravenous antitoxin is the method of choice. In the present paper we will attempt to evaluate the efficacy of antibacterial serum at the present time.

This paper forms a supplement to that of Wright, De Sanctis and Sheplar[6] from this service in 1929. It is based on a study of 75 cases treated with antibacterial serum during the period from January, 1929, to October, 1937.

The experience with these cases leads us to be both critical in our judgment of the accepted method of treatment, and cautious of abandoning it for those perhaps less effective. We are able to show that, when a potent antibacterial serum is properly used, the results are good. In fact, during the last five years we have had no reason to change our methods.

TECHNIQUE OF TREATMENT

On admission a routine blood culture is taken. If a marked petechial eruption be present, smears and cultures are made of these lesions. A spinal puncture is then done, and specimens of fluid are removed for the following routine examinations: (1) cell count and globulin content; (2) stained smear for bacteria; (3) culture; and (4) sugar and lactic acid content. If the fluid proves to be cloudy, intraspinal serum is given at once. As much spinal fluid as possible is drained off, and 20 c.c. of New York City antimeningococcus serum is introduced by gravity.

One intraspinal dose of 20 c.c. of serum is given every calendar day thereafter, until the patient shows definite clinical improvement and

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the culture, chemistry, and cell count of the spinal fluid show a return to normal. Two consecutive negative cultures are obtained before the serum is stopped.

If the patient is very toxic, a second intraspinal dose of serum is occasionally given during the first twenty-four hours. If the patient shows evidence of much intracranial pressure, a second spinal drainage may be done during a day, without giving more serum. It is generally better not to drain until six or eight hours after the previous serum injection.

Intravenous serum is not given unless extreme toxicity, rash and fever indicate bacteriemia. If given, the dose is 20 to 40 c.c. of serum diluted with equal parts of normal saline. Doses are repeated only on persistence of bacteriemia, in such cases generally twice daily.

Intramuscular serum is given only when an intravenous injection is indicated and a vein is not available.

The sera we have used have been those made by the New York City and the New York State Boards of Health. The New York City serum is now used routinely. If improvement does not occur with this after four or five days, a change is made to New York State serum. In this series there was no marked advantage with one or the other. Both sera, as far as we know, have been practically the same since 1928. We have not used commercial sera or antitoxin.

In treating our cases in this fashion, we have used in all 491 doses of serum, an average of 6.8 doses per case and an average of 130 c.c. per case. Intravenous serum was used only in 11 cases and intramuscular injections in seven. When used, these routes were employed generally only once or twice. This was not the procedure in 2 cases of bacteriemia without meningitis not included in the present series. These cases were treated intravenously, approximately with 40 c.c. of serum per day for six days. Each had an uneventful recovery.

RESULTS

Our 75 cases comprise an age range of from 1 month to 11 years with an average age in the entire group of 3.7 years. The average age in the fatal cases was 2 years. In general the patients had been ill 4½ days before admission. There were 15 deaths in the 75 cases, a mortality of 20 per cent.

It is interesting to note that in 7 of the 15 fatal cases there were serious complications not due to the meningococcus. We feel that these conditions are worthy of mention:

1. Bronchopneumonia with hemolytic streptococcus bacteriemia.
2. Massive consolidation of the right lung with staphylococcus empyema. Hydroureter and atrophic right kidney. This case also showed a hemolytic streptococcus in the ventricular fluid.

3. Bilateral mastoiditis and questionable superimposed pneumococcus meningitis.
4. Bilateral bronchopneumonia.
5. Bullous impetigo with bilateral suppurative otitis media.
6. Lobar pneumonia with pneumococcus iridocyclitis.
7. Previous bronchopneumonia of three weeks' duration.

It is obvious that most of these children might well have died in spite of any type of antimeningococcus therapy. In the 8 uncomplicated fatal cases 3 patients died within forty-eight hours after admission, one of them without the diagnosis having been made. It seems therefore that the gross mortality figure of 20 per cent does not give an entirely accurate picture of the results of treatment. Excluding the forty-eight-hour deaths, the total mortality was 16 per cent. If one would be allowed a little more latitude in statistics and exclude those cases with unusual multiple complications, the mortality rate more closely approaches 10 per cent.

We noted in the patients who recovered twelve instances of complications due to meningococcus, eight of which were permanent. They are as follows:

1. Two cases of hydrocephalus with mental impairment.
2. Three cases of iridocyclitis with permanent blindness; two of these were bilateral.
3. One case of bilateral optic atrophy.
4. One case of bilateral nerve deafness.
5. One case of bilateral iritis with recovery.
6. One case of bilateral optic neuritis with recovery.
7. One case of strabismus.
8. Two cases of arthritis with complete recovery.

It is of interest to note that 5 of the 8 permanent sequelae occurred in 1929, 2 in 1931, and the last in 1935. In this connection we observe that the greatest incidence, mortality, and severity of the disease occurred during the years 1929 to 1932. In this period there were 49 cases with a death rate of 24.5 per cent. Since 1933 we have had 26 cases with a mortality of approximately 13 per cent. There have been no deaths in the last 20 cases treated with serum.

SUMMARY

Our results closely approximate the figures reported by Neal[7] in 1933. Her series comprised 302 cases with 57 deaths, a rate of 18.3 per cent. A series of cases summarized recently by Bolduan[8] at Bellevue Hospital also show a comparable mortality. He reported 191 cases from 1928 to 1937 with 26 per cent deaths. From 1929 to 1932 there were 138 cases with 30 per cent mortality. From 1933 to 1937 there were 53 cases with 15 per cent mortality. Taking the greater number of his cases into consideration, the results are quite similar to ours.

The fatality rate in our cases is strikingly lower than in Hoyne's series of 211 cases treated with antiserum, where the death rate was 45.9 per cent. It also compares favorably with a series of 278 cases treated by Schwentker,[9] of Baltimore, where the death rate was 30 per cent. Other authors reported much higher mortality rates in different parts of the country. These figures have been quoted as high as 62 to 80 per cent (Tucker[10]).

Furthermore, the mortality rates of our serum-treated cases and those of Neal and Bolduan appear to compare favorably with Hoyne's series of antitoxin treated cases. The latter group comprises 85 cases with a mortality of 23.5 per cent.

There seems to be little to choose between the efficacy of antitoxin as used by Hoyne and others (Hodges and Shields,[11] Tucker,[10] and others) and the antibacterial serum as used by Neal, Bolduan, and ourselves. We are somewhat at a loss to explain why their mortality with serum-treated cases is so much higher than ours.

As far as the treatment of meningococcus cases with New York City serum is concerned, we feel that the procedure is of considerable value. It is evident, however, that there is still room for improvement. It appears that the low mortality in the past few cases might very well be due to a decreased virulence of the infecting organism. The mortality of the first four years of our series was almost twice as high as for the latter period; yet both the serum and the method of treatment were the same. This was also noted by Bolduan.

It goes without saying that early diagnosis is of prime importance. Our patients who died had been ill on the average one day longer before admission than those who recovered. It may well be that delay in treatment, even for such a short time, has a great bearing on the outcome.

Potent serum must be used. This is not such an obvious point as one might at first suppose, and it may in part explain some of the higher mortality rates in serum-treated cases. There are at present, unfortunately, no laboratory methods which will indicate the clinical potency of a serum in a given case. De Sanctis and Sheplar showed clearly that the only reliable test of the serum is its therapeutic effect. Agglutination titers have no relation to clinical potency. It is of prime importance that the serum used be obtained from the strain of bacteria which is causing the case under treatment. It is also of importance that the serum not be made from bacterial strains which have been so long on laboratory media as to have diminished their antigenic properties. In the clinical handling of the case if one does not obtain satisfactory improvement within a period of a few days, another brand of serum should be used.

We are strongly of the opinion that intraspinal administration of serum is essential. This, however, should not be done at too frequent intervals. In our cases a single daily injection of 20 c.c. has been most

effective. More frequent injections offer no advantage. This is borne out by the fact that Bolduan's cases were treated on the average twice as frequently as ours (every twelve hours), yet the results were almost identical. Neal has the impression that more frequent injections may have a deleterious effect.

There are some, chiefly Hoyne, who maintain that meningitis is a phase of a generalized meningococcus infection, the most important lesion being bacteriemia with toxemia from bacterial products. Bacteriemia has not been a prominent feature of our cases. Routine blood cultures were done on 41 patients, of which only 11 were positive. Five of these 41 patients died. Of the 5 patients who died, 2 had bacteriemia, and 3 had not. Neal also reports only 3 positive blood cultures in 43 early cases.[12] Furthermore, when bacteriemia was present, it was generally transient and rarely persisted beyond the second day of treatment. There are a few cases in which bacteriemia does occur without meningeal involvement or with a very mild meningitis. We had three cases of this type not included in the present series. In the great majority of cases it would seem that the massive infection of the central nervous system is of paramount importance, while bacteriemia is coincidental and not of primary importance. Certainly a very conspicuous aspect of the pathology is the thick, obstructive, fibrinoplastic exudate involving the meninges. It is also true that the most feared sequelae of the disease are those involving the brain and cranial nerves, namely, obstructive hydrocephalus, mental deterioration, optic atrophy, iridocyclitis, and nerve deafness.

We would therefore hesitate to abandon intraspinal therapy in favor of an exclusively intravenous type of treatment, whether antitoxin or antibacterial serum were the therapeutic agent in use. We have had only slight personal experience with the use of sulfanilamide in treating meningococcic meningitis. The first case in which we used this agent as the sole method of treatment resulted in fatality. As we had previously treated 18 consecutive cases successfully with serum, we were discouraged from continuing the sulfanilamide as the sole therapeutic agent. We have, however, used this material in conjunction with serum in a few cases not included here. We have been unable to note any striking effect attributable to this drug. The number of cases, however, has been too small to warrant definite conclusions.

Schwentker reports 330 cases, 52 of which were treated solely with sulfanilamide, the remainder being treated with serum. He had very much better success with sulfanilamide, the mortality rate being 15 per cent, whereas in the serum-treated cases it was 30 per cent. While this is an interesting series of cases, the superiority of sulfanilamide is not conclusively proved. Schwentker himself pointed out that the cases treated with sulfanilamide were those occurring after that particular epidemic had been on the decline, a fact which would tend to produce

lowered mortality, no matter what the treatment. In the second place, complete control is lacking in that alternate cases were not used. While not conclusive, the results of sulfanilamide are striking, and the treatment obviously warrants further trial.

It evidently has a beneficial effect upon meningococcus infections and its administration simplifies the treatment of meningitis. It is possible that this may be the method whereby the number of intraspinal treatments may ultimately be reduced. Although sulfanilamide itself may be introduced into the spinal canal in solution, a concentration of the drug can be maintained in the spinal fluid by oral administration alone. While, at the present time, we feel that antibacterial serum properly used is the method of choice, we hope that a more thorough trial of sulfanilamide will be forthcoming in order to definitely determine its usefulness. We can see no objection to combining sulfanilamide with serum treatment.

CONCLUSIONS

Meningococcic infections in children can be treated effectively with antibacterial serum.

Intraspinal administration of serum is essential except in cases of bacteriemia without meningeal involvement.

The conservative method of therapy discussed is the method of choice.

Repeated intravenous injections of serum are indicated only in persistent cases of bacteriemia.

Intramuscular serum injection is very rarely indicated.

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CONGENITAL OMPHALOCELE

A Report of Four Cases

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THE rarity of congenital omphalocele or congenital umbilical hernia justifies a report of four such cases. Its incidence is approximately once in 10,000 deliveries when both liver and intestines are outside of the abdomen. When intestines alone are found in the rupture, the incidence is somewhat greater, occurring once in every 5,000 deliveries.[1]

The digestive tube (primitive gut) and ventral body wall are formed primarily by a bending ventrally and fusing of the originally flat germ layers which rest upon the yolk sac.[2] The splanchnopleure on each side first bends ventrally and fuses with its fellow of the opposite side in the medial line to form the gut. Soon afterward the somatopleure likewise fuses in the ventralmedial line to form the body wall.[3] It is clear that a defective fusion of the two sides of the somatopleure would result in a more or less extensive medial cleft. The cleft may extend from neck to pelvis, giving rise to a stillbirth, or may be limited to a small portion of the abdomen or thorax.

When the cleft involves the entire abdominal wall, it is known as gastroschisis completa. In a lesser degree of fission parts of the abdominal viscera covered with peritoneum may protrude through it and form what is known as omphalocele.

The development of the intestines and liver takes place for the most part outside of the body wall after the bending of the somatopleure. The organs are covered with mesoderm and attached to the body by dorsal mesentery. It is clear that a failure of regression of the organs to their normal position is an important factor in maintaining the abnormal breach in the abdominal wall.

Many factors have been mentioned as producing causes of this abnormality.[4, 5, 6, 7] Scarpa suggested traction on the umbilical cord. Cruveilhier suggested that undue pressure in the abdominal region because of faulty fetal position may be a factor. Ohlfield accused a pulling of the vitelline duct on the intestines in the root of the umbilical cord. Other factors suggested are an inhibition of growth of the abdominal wall, a disturbed relationship between growth of the abdominal cavity and its contents, and accidental bands of adhesions. A more thorough description of such defects is found in the works of Bardeen and Watson. There is no familial tendency in this defect of development.

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In this series of four cases only one presented liver along with intestines in the rupture.

CASE 1.—A strangulated umbilical hernia, containing small and large bowel, is shown in Fig. 1; prematurity. A primipara, aged 24 years, delivered spontaneously of male twins in posterior position after a right mediolateral episiotomy was performed.

The twins were definitely premature, having been delivered at least one month before term. Birth weights were 4 pounds 5 ounces and 4 pounds 11 ounces, respectively. The first twin presented a massive omphalocele described as follows:

A large cone-shaped mass with its apex at the umbilicus contained what appears to be a strangulated loop of intestine through a peritoneal protrusion at the umbilicus. The remainder of this mass (size of a small orange) contained dilated umbilical veins, umbilical artery, and a large amount of Wharten's jelly. This was the result of the fact that the ligature was placed distal to the umbilicus for fear of constricting the hernial protrusion.

An immediate operation was advised, and eight hours after birth the infant was submitted to surgery. At operation (under local anesthesia) there was found a

Fig. 1.

large strangulated umbilical hernia whose contents were the lower eight inches of ileum, the cecum, the appendix, and two inches of ascending colon. The colon and cecum were adherent to the parietal peritoneum. The intestine was discolored but not gangrenous. The mesentery of the bowel was edematous and engorged. The intestines had herniated themselves through a small hiatus in the transversalis fascia about one-half to three-quarters of an inch in diameter.

The operation[s] consisted of division of a firm vilimentous senechia which bound the cecum and ascending colon to the peritoneum. A modified Blake hernial repair was performed.

Recovery was uneventful, and the child was discharged within eight days, weighing 1 pound and 1 ounce above birth weight. This child has been followed for three years and has retained a firm abdominal wall without signs of recurrence.

CASE 2.—Prematurity; omphalocele containing liver, gall bladder, and intestines. F. G., aged 29 years, pre-eclamptic, was delivered one month premature.

Infant, B. G., was born with a large omphalocele about the size of a fist. Operation was performed on the same day under ether anesthesia. An incision was made over the upper and lower angles of the hernia, and the sac was opened. Within the sac was found the liver which appeared larger than normal. The gall bladder and intestines were normal. All of these organs were replaced into the abdominal cavity. The plastic repair was then performed.

The post-operative course was uneventful.

CASE 3.—Full-term child; omphalocele containing appendix.

M. S., aged 26 years, para iii, gave birth spontaneously to a female child which had a rupture at the umbilicus.

The patient was operated nine hours after birth under ether anesthesia. A circular incision around the base of the umbilical cord revealed a peritoneal sac containing appendix which was adherent to the sac. The sac was opened, and the appendix was released and replaced in the abdominal cavity. A plastic repair was then performed.

The patient made an uneventful recovery and was discharged as well ten days following operation.

CASE 4.—Congenital omphalocele containing small intestine.

E. E., para ii, delivered spontaneously of a full-term female infant weighing 7 pounds 10 ounces. The infant presented a mass about the size of an orange. Operation was performed on the same day under nitrous oxide anesthesia. The contents of the sac consisted of several loops of small intestine which were replaced within the abdominal cavity. The breach in the abdominal wall was then repaired.

Recovery was uneventful.

From these reports, one notes that not a single patient had succumbed. This was no doubt because of the fact that the cord was properly tied so as to exclude the contents of the sac. In addition, each of these patients was operated within twenty-four hours of birth so as to prevent peritonitis.

CONCLUSIONS

Four cases of congenital omphalocele or congenital umbilical hernia of various types are reported. Each of these patients recovered completely, and the defects in the abdominal wall were closed. The development of the primitive gut and the abdominal wall is discussed. The importance of proper ligation of the cord is stressed, as is also the need of early operation.

We are indebted to Dr. William Wolfson for permission to report Cases 2, 3, and 4.

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Critical Review

ALLERGIC DISEASES

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Nothing is more enjoyable to the man who has made science his career than to increase the number of discoveries, but his joy is complete if the result of his discoveries is put to immediate practical use.—PASTEUR.[1]

The individuals, conducting an investigation, should have had the opportunity of seeing disease in all its phases, and of observing the symptoms it produces.—MACKENZIE.[2]

THE study of allergy developed largely through the necessity of relieving patients. Clinicians dealing with allergy have shown more than usual interest in fundamental theory and causes and have certainly increased the general fund of information. However, their need for making a living has resulted in extreme pragmatism and a dangerous rapidity in handling the clinical material. Hence they have been unable to clarify basic principles. These basic principles will more likely be understood when chemically purified antibodies, such as Heidelberger[3] is obtaining, replace the heterogenous mixtures now used clinically.

The literature soon will show a growing separation between investigators in the realm of theory and the reports of clinicians. This tendency, of course, will parallel that taken by the basic medical sciences and yet has unfortunate consequences. It often leads to a mutual distrust between "laboratory men" and "mere clinicians" and necessitates interlocutors at the very time that medical educational policy seeks a greater coordination.

Since the previous review, *Clinical Allergy*, a textbook by Tuft,[4] has made its appearance. Although the title implies only clinical aspects, the author has very successfully presented current theoretical and experimental material and has taken a broad viewpoint on nomenclature and classification. The chapter on allergic dermatoses is particularly well done. In considering sensitivity to endocrine products, it seems unfortunate that the author did not draw more from his own observations since he contributed so largely to our knowledge of insulin sensitivity. The chapter on allergy in children is disappointing. The author quotes so liberally from Bray[5] as to leave the reader dependent on the latter's views. Tuft also stresses similarities between adult and juvenile allergy not always acceptable. The newer recognized importance of inhalant sensitivities in the young is neglected; the emphasis is on the time-observed importance of foods. The discussion of thymic asthma is in keeping with the present knowledge of the thymus. There is, however, no mention of *eczema tod.*

Regarding basic theory several reports deserve mention. A study of tuberculin allergy produced by parenteral B.C.G. administration is reported by Kereszturi, Rosenberg, and Park.[6] Allergic response was produced in 80 per cent of the patients by intracutaneous inoculation

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and in 62 per cent by subcutaneous inoculation. The allergic development varied with the severity of the local reaction and the reaction of lymph nodes but showed no relation to age or previous vaccination (immunity?). It will be recalled that Rich[7] challenged the usual acceptance of allergy or sensitivity phenomena as an integral part of the development of immunity. From his studies in bacterial allergy, as illustrated by tuberculin sensitivity, he finds much to justify separation of sensitivity from immunity development. In the review of his thesis[8] appearing in the French literature, some of his points are as follows: With tuberculosis as a type of infection he notes: (1) the inability of allergic inflammation to protect in the absence of specific acquired immunity; (2) the development of immunity without concomitant hypersensitivity; (3) the separation of immunity from hypersensitivity by desensitization in acute nontuberculous infections; and (4) the persistence of immunity after loss of hypersensitivity, showing a lack of parallel or interdependence.

Bronfenbrenner[9] has presented the relationship of immunity and allergy and takes his place with von Pirquet, Schick and others in the opinion that "the phenomena of specific heightened resistance and of heightened susceptibility are different manifestations of a single biological process—allergy." Specific heightened resistance represents the process affecting the antigen. Heightened susceptibility represents the process involving the tissues of the host. Both processes may occur in a single event whenever the antigen is reintroduced into the previously exposed (allergic-immune-sensitized) animal.

Even in the clinical field of allergy we may find use for Bronfenbrenner's theory, as illustrated by infantile eczema. Lippard[10] pursuing the work initiated by Schloss[11] and the Cornell group, compared in eczematous and normal infants skin tests and precipitans for egg and milk. When the normal infants had received neither of these foods, the tests were negative. Several infants showed positive tests when they received large amounts of these foods, whereas some eczematous infants showed pronounced tests even when they had never been given the offending foods. (As two of seven eczematous infants showed skin tests parallel with those of the mother, Lippard found evidence supporting placental or breast milk transmission of sensitivity.) If the infants were then given the foods the tests were fortified or intensified and persisted for a longer period. From this it would seem that the sensitive (eczematous) group present only an exaggeration of the normal response, or, as Bronfenbrenner put it, heightened tissue response. If this be true then, of the three hypotheses earlier advanced by Lippard, Schloss and Johnson,[12] the "neutralization by some unknown immune mechanism" would account for the degree of difference between "normal" and "sensitive."

Some such neutralization mechanism may be involved in the phenomena reported from Cooke's clinic.[13] First mention of this work was made two years ago, when Cooke[14] reported a protective factor in the blood of hay fever treated patients. The blood or serum contained a substance which apparently reduced or blocked passive transfer. During the past year these findings have been more completely studied by Cooke and his associates. In a group of nonsensitive volunteers the investigators injected ragweed extract with ragweed sensitive serum. There were no serologic changes noted. In another group larger amounts

of ragweed extract were injected alone. Serologic changes were found resembling those observed in ragweed-sensitive patients after treatment. The inhibiting agent was specific for the pollen involved and was contained in the pseudoglobulin of the serum. The neutralization technique was adequately controlled with normal serum which obviated a criticism of the initial reports.

A similar blocking substance in sheep serum is reported by Cohen and Nelson.[15] Repeated injections of ragweed extract induced the development of the substance which blocked passive transfer of ragweed sensitivity. The technique differed somewhat from that used by Cooke and his associates, but, since they have also confirmed Cohen and Nelson's findings, more of the variants inherent in the Prausnitz-Küstner technique are eliminated. No report has been made concerning possible therapeutic significance of the sheep serum.

From the field of animal experimentation comes also a report by Pratt[16] on anaphylaxis in multiply sensitive guinea pigs. Using egg albumin and horse serum as antigens, he obtained a single not a summation effect. He suggests that the body can react to only one antigen at a time (anaphylactically) or that the relative size of antigen molecules allows the smaller to react with greater speed.

In the 1936 review mention was made of the studies of Benjamin and his co-workers,[17] reporting the activation of ragweed filtrate with adsorption linkage on larger colloid molecules. This year Long and Teller[18] have verified the findings and believe that considerable knowledge regarding the nature of antigens can be obtained through further inquiry along these lines. A study of the influence of epinephrine upon antigen and antibody action is reported by Tuft.[19] Epinephrine delays absorption of an injected antigen but does not interfere with specific immunologic action. From this it would seem logical that epinephrine can be used in preventing marked reactions from any type of allergen where large dosage or rapid administration is indicated, as for example, in the "desensitization" of serum-sensitive patients preparatory to the administration of antiserum.

Another study of antigens is that of Dorfman and Efron,[20] who report the effect of serial dilution of the testing extracts on the skin tests. They find "discontinuous" plateaus in all ranges of concentration and conclude that extreme caution must be taken in applying comparative skin tests to the quantitative evaluation of antigenic activity. This word of caution seems applicable to all studies in which the skin test is interpreted for either antigen or antibody titers.

This reviewer has never found in his experience with children (compare "Allergic Diseases of Childhood"[21]) that the leucopenic index has been of value. During the past year exhaustive studies have shown it to be of no value in any field of allergy. Hill and Nethery[22] reported variations in the leucocyte count in relation to leucopenic index and called attention to technical errors and physiologic factors in spite of which a standard technique could be achieved. They did not report studies on or application of the standard technique. Brown and Wadsworth,[23] however, made a careful study with all their special statistical formulas and conclude that there is no adequate proof of either a normal postprandial leucocytosis or a postprandial anaphylactic leucopenia. Loveless, Dorfman, and Downing[24] combined a report on standardization and application of technique. They too failed to confirm leuco-

cytosis as the normal response to ingestion by either level or fluctuation of the white cells. They find no support for the use of leucopenic index in detecting incompatibilities of foods. A few observations with the technique also showed no significant change in the leucocyte level or fluctuation when asthma was induced by injection of ragweed extract.

Biophysical studies have been vogue in medical research for some time. In allergy the search for constitutional allergic types or for linkage of physical and chemical findings with allergy has not been very successful (compare previous review[25]). During the past year T. Wingate Todd,[26] with his rather unique institute for studying developmental growth patterns, finds an "aid" in roentgenographic and psychologic studies for appreciation of the effect of allergy on constitution. Cohen and Friedmar,[27] with Todd's stimulation, report the roentgenographic scoring of long bones as a guide to appreciation of food allergy in children. This is a refreshing challenge. Granting the effect of gastrointestinal disturbances on mineralization, the method of exclusion by which allergy is incriminated leaves much to be desired. It will be interesting if others can find use for the methods suggested by Todd.

Blood chemical studies are reported by Bloor, Blake, and Bullen.[28] Unlike Hansen and his co-workers[29] reporting on infantile eczema, they find no difference in the unsaturated fatty acids of normal persons and individuals suffering with hay fever and asthma. A difference of saturation degree was found in the various types of fat which confirmed their previous hypothesis regarding the function of cholesterol in the metabolism of fatty acids. Chobot and Dundy[30] studying blood cholesterol in allergy found no evidence that the cholesterol level could be used as a guide for thyroid administration and for that matter concluded there was little basis for thyroid therapy.

Surface tension, sedimentation rate, and blood pressure change following ingestion of allergenic foods were noted by Sullivan and Vaughan.[31] No striking variations occurred. A more novel approach was that of Anderson,[32] who found a consistent difference in the colloidal gold curve obtained from serum of allergic individuals. He conjectured that a lack of some protein factor in the allergic person made for this contrast with the normal gold curve. The study warrants further pursuit.

Rabbit blood was analyzed by Wenner and Buhrmester[33] for potassium changes associated with anaphylaxis. Presumably acetocholine is released with the potassium, but bioassay is necessary because of its minute amount. The cat's blood pressure response to injection was used for the assay. These workers suggest acetocholine is of greater import than histamine in shock. (It should be remembered that Lewis's theory carefully used the term histamine-like substance.)

The monkey is apparently a missing link so far as the relation of allergy and anaphylaxis is concerned. The Division of Applied Immunology at the Jewish Hospital of Brooklyn is to be envied for the support which enables them to use this costly experimental animal. Since Strauss[34] showed that the skin of the monkey could be passively sensitized with human serum, many more studies have been made. Strauss and Walzer[35] have reported the technique for demonstrating intestinal absorption of antigens. In his review, "Physical Allergy" Walzer[36] gives an excellent survey of monkey experiments in which his department has had so large a share. The animal does not give direct skin tests, but apparently is a satisfactory recipient for passive transfer

Although Kopeloff, Davidoff, and Kopeloff[37] reported anaphylaxis production in monkeys, Albert,[38] working in Walzer's department, found the essential criteria for his experiments in this field lacking. Walzer logically hesitates to accept without reservation the technique used by Kopeloff and associates. Caulfeild[39] at Connaught Laboratories reported transfer of sensitized guinea pig serum to the skin of the monkey with the resulting positive skin transfer of tests. He thus identifies the experimental antibody of anaphylaxis with that occurring in the allergy of man. Walzer leaves the proposition of heterologous serum transfer an open question.

At the most recent meeting of the Division of Applied Immunology (reported to me by a colleague) Walzer[40] demonstrated skin and mucous membrane sensitivity transfer in monkeys. However, since Schultz-Dale tests with intestinal smooth muscle were negative, it was concluded that the mucous membrane was the more likely shock tissue when the sensitizing serum was from patients with asthmatic or gastrointestinal symptoms. With this latter as a premise, antispasmodics would be less valuable therapeutically than drugs to reduce edema, as for example aminophyllin. At the same meeting Grolnick, Bowman, and Walzer[41] reported on their study of contact dermatitis. A specific wheal they had found leaves the skin more responsive, whereas histamine lessens the response to subsequent whealing. They now report that the sites of whealing differed with regard to subsequent erythema from which they conclude there is either an inhibitory factor or a mechanism for erythema independent of that for wheal formation. The other Walzer[42] reported successful passive transfer induction by rubbing a cottonseed-lanolin mixture on the sensitized area. In discussing this report Sulzberger[43] and later Coca[44] suggested that no special hapten or intermediary excitant was involved. They felt that wheal reactions may occur in sensitive patients handling the offending substance but that such patients need not give positive patch tests. Mention should be made at this time of the study by Strauss and Coca[45] on contact dermatitis experimentally induced in monkeys. By a circular incision the skin of the arm preceding and distal to the application of the oil extract excitant, they induced a local tissue reactivity unrelated to bloodborne antibodies. The sensitizing application was maintained by a cast. subsequent patch tests at the site of inoculation confirmed Coca's reiterated thesis of local tissue reactivity.[46] In discussing this paper Landsteiner[47] suggested that hapten formation might well be concerned as in the case of drug allergy.

Sherman, Kaplan, and Walzer[48] successfully transferred sensitivity to the nasal mucous membrane. Using the anterior tip of the inferior turbinate and septum, they obtained response to intravenous, subcutaneous, intranasal and topical applications. In the same series of studies on mucous membrane sensitivity, Gray and Walzer[49] applied the technique to sites of transfer in the rectal mucosa and skin. Characteristic edema, hyperemia, and mucous secretion were obtained as was also the subjective symptom of pruritis. It would seem that the possible sites for passive transfer to mucous membrane had now been exhausted.

Stull, Sherman and Cooke[50] have made a finer differentiation of the skin-sensitizing antibody of allergic serum. By application of the technique of Harris and Eagle,[51] these studies show the active principle to

be in the pseudoglobulin. In untreated patients they detected a qualitative alteration of the fraction. From the same clinic Sherman and Stull[52] studied the specificity of skin-sensitizing antibodies as shown by neutralization with antigens. They found neutralization frequent, but reciprocal cross neutralization occurred only with closely related antigens. Somewhat similar reasoning was used by Pratt[53] to account for the single response of anaphylaxis in multiple sensitization of guinea pigs. It would seem that the previously accepted thesis of addition or summation effects for clinical allergic manifestations, also may be open to doubt.

Grubb and Vaughan[54] studied group antigen reactions. This has long been a controversial subject. These newer studies are not as detailed as those previously discussed, regarding giant and dwarf ragweed antigens. These authors found common factors in families but no single pollen representative of the entire group. Redtop reacted most frequently with other grasses and dwarf ragweed with other composites. Workers from the Pacific Coast will for the most part agree with the inference that there is no group specific or shortcut in testing and treating for hay fever. Grubb and Vaughan mark with surprise the long-observed phenomena of positive skin tests to pollens which the patient never encounters. The grouping tendency is shown in the number of patients with food intolerance and positive skin tests to pollens of those food sources.

These observations lead us to the report by Stier and Hollister[55] concerning oral administration of pollen for the treatment of hay fever and for that matter to Urbach's use of leaf and stem extracts instead of the more expensive pollen.[56] Both methods are claimed to be successful. Time will tell.

Allergy was the subject of one of the panel discussions of the 1938 meeting of the American Academy of Pediatrics.[57] Piness, relying on a statistical listing of skin test reactions, challenged Rowe whose elimination diet often tends to discount the significance of skin tests. In turn, Ratner and this reviewer felt that there were such considerable variations in allergy as to warrant the terms "major" and "minor" allergy while Piness clung to the "all or none" theory.

Ratner's recent article,[58] "Allergy in Childhood, Modes of Its Acquisition," is excellent. A rapid review of the experiments concerning the nature of allergy leads up to his own contributions, i.e., induction of asthmatic phenomena in guinea pigs by inhalation and ingestion rather than injection. From this it is evident that he follows those who find a common basis in both man and animals. It is hoped that the same technique will be applied to monkeys. Ratner also believes that all individuals are capable of developing allergy. For support he suggests that circumstances (infection, etc.) may lower the barriers against foreign protein absorption. This may be true to some degree, but it should be pointed out that nonallergic recipients of passive transfer will show adequate absorption of the antigen from the gut without additional irritation being present. There is room then for some possible protective mechanism similar to the blocking substance of Cooke,[59] which prevents the normal person from developing the marked sensitivity of the allergic person.

In his second paper Ratner[60] applies his studies on congenital or intrauterine sensitization. He advocates diet control to avoid likely

sensitizing foods. The program is a practical one but calls to mind the difficulty of complete acceptance of placental transmission in the face of glaring contradictory evidence.

There comes to mind quickly an example of two parents (both physicians): the father is markedly allergic, the mother entirely free, while both offspring have followed the paternal pattern since early infancy. The reviewer holding no brief for early introduction of varied foods, finds certain clinical experience contrary to the theory that early ingestion fixes a sensitivity. He has seen several instances where tomato (for which Piness[61] finds the most frequent positive skin test) introduced as an antiscorbutic was followed by skin manifestations suggesting a minor allergy. In some instances the food has been continued with a gradual waning of the symptoms; in other cases the administration of the food was discontinued until a later date at which time there was no reaction.

It would seem that degrees of sensitivity reflect a possible germ plasm inheritance, where perhaps the tissue response is not checked by "protective bodies." A parallel might be drawn in the matter of diphtheria immunity, there being some individuals incapable of forming antitoxin in response to either the disease or its prophylactic agents.

As illustrative, perhaps, of the "specialization of the day" might be mentioned Ratner's program for elimination of eggs in the diet during pregnancy, which appears simultaneously with an obstetrical report[62] advocating a diet rich in eggs for treatment of nephritic toxemia. It would be interesting if such forced feedings were accompanied by an increased incidence of egg sensitivity in the offspring.

Kibler[63] presents another discussion of intractable asthma. He used diary study with elimination diets. Less acceptable to the reviewer is his use of intranasal tests and iodized oil. That he should attribute loss of food sensitivity in children to outdoor life is hard to accept with the known relationship to time-age changes. His use of avertin is a valuable suggestion.

Local skin reactivity to bacterial filtrates has been studied by Shwartzman and Morell.[64] They discuss ultrafiltration, cataphoresis, and ammonium sulfate precipitation in methods of preparation. Dialysis, however, was found the best procedure to eliminate nonspecific reacting substances from the bacterial extracts. The reviewer awaits the application of sonic vibration and lyophile freezing as adjuncts in the preparation of more concentrated bacterial antigens for testing. Intracutaneous injection of scarlet fever toxin was considered by Kern, Crump and Roddy[65] to immunize against scarlet fever. The skin undoubtedly is very important in immunization, but some might feel that scarlet fever is an unfortunate disease on which to base immunity solely by the Dick test.

Clinical reports continue to fill most of the literature with inevitable repetition. An illustration is Hill's discussion of milk sensitivity in eczema.[66] While he makes a strong plea for milk substitutes, as for example sobee, he finds it "very difficult to evaluate the efficacy of any therapeutic procedure in infantile eczema." And again "there is still a great deal to it that is hazy and obscure." Hill,[67] in another report, is prone to discount inhalant factors, yet Zakon and Taub[68] report again the likely role of inhalation of house dust and horse dander in the etiology of atopic dermatitis. In the 1936 review[69] it was implied that vegetable protein might not be so desirable a source

as one of animal origin. Rittinger and his co-workers, however, found it adequate. In the last year Basu[70] reported experiments from which he concluded that as a sole source of protein soy bean is incomplete and unsuitable for rats.

A general review of diagnostic methods and programs for handling allergy in practice is presented by Criep.[71] Somewhat similar is the paper, "What Every Physician Should Know About Allergy" by Harvey.[72] His diet program he labels "food addition method." He also discusses the use of adrenal (Pottenger), pancreas (Oelgetz), thyroid extracts, which have been mentioned in previous reviews.

Skin manifestations are the subject of two reports by Seyler.[73] The first considers eczema, atopic and contact types. Atopic eczema is illustrated by the disseminated and infantile types and usually is accompanied by positive scratch tests. Contact eczema is illustrated by dermatitis venenata and occupational dermatitis in which the patch test is used. His second paper[74] discusses vesicular eruption on the hands due to such excitants as dermatophytids, bacterids, and external irritants. Food allergy in relation to diseases of the skin is rather exhaustively treated by Hopkins.[75] It is surprising to note that the author rarely relates chronic urticaria to foods, or eczema of infants to contact irritants. Levin,[76] in contrast to Hopkins, considers food, inhalants, and contact irritants related to eczema. In a second paper[77] this same author discusses trichophytids as etiologic factors with foods. He offers two case studies where a course of treatment with trichophytin extract was beneficial. Blumenthal[78] reviews eczema, urticaria, and allied dermatoses using the extensive classification of Rossle.[79]

Of bizarre reports that of Niles[80] reporting two instances of dermatitis caused by shoe leather is interesting as patch tests were positive, and phytid, dye, or tanning chemicals apparently were ruled out.

Barlow's discussion of asthma in children[81] is not remarkable except as it presents the aspects observed in the antipodes. Spain's discussion[82] is of considerable value. The reviewer is in particular sympathy with the contention that the problem is a pediatric one, that skin tests may be negative, and that general health measures must not be neglected in the search for specific programs. He wonders, however, that Spain encounters such a high incidence of respiratory infection at the beginning and end of asthmatic attacks. Their occurrence has been far from constant in the reviewer's experience, and he has not always been sure that true infection is typical (compare Miller and co-workers,[83] "Allergic Pneumonia").

Weil's two reports[84] on hay fever in Alabama are the first the reviewer has noted from that state. The importance of pecan which is compared with ragweed has not been emphasized by others. The tree pollinizes in April, May, or June and the pollen gives skin tests and satisfactory results in treatment. It seems strange that similar importance is not attached to the tree in Texas and other pecan-growing areas. It may be expected to assume importance in those sections of California where pecans are being planted commercially. Weil finds ragweed, cocklebur, the plantains, and amaranths important. Instances of grass pollinosis apparently are rare. His second report is a rather cursory correlation of flora and pollen survey for clinical guidance.

Autogenous vaccines are advocated by Behen[85] with the neat term "collateral immunization" in hay fever. The author claims such vaccines from nasal cultures control exacerbations during the hay fever season but this seems to the reviewer quite possibly a nonspecific effect (compare previous reviews). The same would apply to Brown's report[86] "that any allergic disease which is due to bacterial sensitization can be successfully treated with vaccine and filtrates."

Gastrointestinal allergy is the subject of a paper by Hinnant.[87] The author has a sane conservatism and advocates careful diagnosis and the ruling out of organic disease. Skin tests are considered only in relation to observed importance; a palatable diet and control of nonallergic conditions are advocated.

Mitchell[88] presents an interesting consideration of potential allergic episodes coincident to the holiday season. The insidious acceptance of known allergens is likely to occur especially in children with relaxed supervision.

Harris,[89] in discussing molds as a cause of allergy, suggests that a history of mushroom intolerance may be important. Tests and treatment are based on Feinberg and Little's studies.[90] An interesting review[91] of 62 cases of allergy due to acetylsalicylic acid observed at the Mayo Clinic showed 44, or 70 per cent, had associated asthma. This is surprising to the reviewer who up to this time had not exercised any particular caution in the use of the drug for asthmatics. Lintz[92] also believes that multiple sensitivity is the rule in allergy and various tracts of the body may be "shock organs," with the skin usually involved as evidenced by positive tests. The reviewer wonders if the author has followed many infants with eczema through a span of time such as witnesses a distinctly lessened skin response (test and eruption), increased respiratory symptoms, and the exclusion of the eczema.

Dean and his co-workers[93] discuss Ménière's syndrome, allergic rhinitis, and eczema of the external canal. The report is not particularly convincing. Echoes of iontophoresis are still heard. Cottrell[94] claims adult cures and only a few failures. We hope he will give a follow-up report after three or five years. As might be expected, another disease is suggested as allergic. Robinson[95] reviews the various theories regarding uremia, cites the similarity of histamine shock to uremia, and hypothesizes a possible allergic basis for uremia.

An interesting correlation of clinical and pathologic findings in bronchial asthma is reported by Thieme and Sheldon.[96] In seven postmortem studies on patients who died of status asthmaticus, they found hyaline thickening and hypertrophy of musculature of the basement membrane of medium-sized bronchi, mucinous plugs in large and small bronchi, and eosinophilic infiltration. The report and illustrations are standard for comparison. The authors wisely admit these results are found in the chronic cases of long standing and that the pathology may not be definite despite definite clinical evidence. We must still consider the disease primarily functional. One cannot tell by pathologic examination the immune from the nonimmune or the allergic from the nonallergic. Harkavy[97] has pursued his interest in tobacco sensitivity and thromboangiitis obliterans, adding biopsy studies. He refutes the arguments of previous critics that tobacco acts nonspecifically (like histamine) and shows allergenic reactions in susceptible patients. Clinically, arrest of symptoms followed with-

drawal of tobacco in 12 patients. Subcutaneous injection of tobacco extract in one patient precipitated a delayed eczematous response and symptoms of thromboangiitis obliterans.

Periarteritis nodosa, a somewhat rare entity, is perhaps allergic according to Berger and Weitz.[98] Muscle biopsy furnished the basis of their diagnosis, as no subcutaneous nodules were present in the case they report. The patient presented evidence of known allergic reactions from which they reasoned the periarteritis might be related.

Various new as well as old familiar antigens are reported in the literature of the past year. Two cases of insulin sensitivity prompted Cohen and Simon[99] to review the literature and present their ideas. The report is not as valuable as that previously made by Tuft.[100] Pendleton, Ball, and Rhode[101] report reactions caused by sensitivity to pituitary extract. More novel to the reviewer is the report by Criep[102] on allergy due to liver extract.

Jamieson's study[103] by skin test of nasal allergy attributable to the housefly adds its inhalant to that of the caddis fly described by Figley[104] and those of the series of lepidoptera reported by Parlatto.[105]

Piqueria pollen was responsible for the seasonal and occupational distress of a nurseryman under Langley's observation,[106] and Weston[107] incriminates derris root as a potential allergen used in insecticides. The latter report, however, gives passive transfer studies which make it more convincing.

Rackemann, Randolph, and Guba[108] in the study of fungous allergy report a specificity similar to that observed in pollen sensitivity. The patients reacted specifically to *Cladosporium fulvum Cke.* but showed no reaction to other species by direct or passive transfer tests. Following Feinberg and Little's technique,[109] Schonwald[110] in Seattle compiled charts of the seasonal tides of allergenic molds in the Pacific Northwest.

Chloral hydrates by mouth or by topical application can produce an eczematous dermatitis which is shown by the report of Baer and Sulzberger.[111] With Goodman, Sulzberger[112] also started a comprehensive series of discussions on acquired sensitivity to chemicals. This discussion, presented at the 1937 meeting of the Association for the Study of Allergy, deals with eczematous sensitivity to clothing and to cosmetics. This profusely illustrated article calls attention to the frequency of dyes as the etiologic factor. Coca's discussion[113] of this paper is valuable; that of Simon[114] is bizarre.

Coca's method of treatment by the use of oil extracts apparently is ideal for pollen dermatitis, according to Rudolph and Deutsch.[115] The reviewer has waited to hear such a report, as the usual treatment acceptable for hay fever leaves much to be desired. Molitch and Poliakoff[116] prevented the occurrence of dermatitis venenata (due to poison ivy) in a sufficient number of children to substantiate the claims for this procedure. Forty-three of fifty given one or two injections of poison ivy extract (oil or alcoholic) were protected, and all members of a control group of thirty-nine developed the disease.

In the field of therapy the report of Boyer[117] suggests propadrine as a valuable adjunct in treatment of allergic symptoms. Prickman and Koelsche[118] found little benefit from the use of suprarenal cortical extract in the treatment of asthma and related conditions, which finding confirms many previous reports regarding this endocrine therapy. As was implied earlier in this report, if Walzer's theory[119] is correct,

that mucous membrane may be involved more frequently than smooth muscle, therapy should be so influenced. The report by Herrmann and Aynesworth[120] showing the efficacy of aminophyllin seems apropos. Criep and Hampsey[121] put an end to the rumor that iodized oil per se has any value for bronchial asthma. They review the literature and present a questionnaire survey.

Waldbott[122] reviews the emergency program for handling severe asthma. Nothing new or startling is found in the report. In their pathology study of asthma previously cited, Thieme and Sheldon[123] emphasize the danger of morphine and atropine as therapeutic drugs for bronchial asthma. Intravenous hypertonic dextrose with epinephrine was found by Keeney[124] to be valuable for six patients with status asthmaticus. Dextrose also was used by Stoesser and Cook,[125] who consider it effective not because of hypertonicity but because of the vague adrenal-carbohydrate factor. This reasoning has seemed fallible to the reviewer as mentioned in previous reviews.

In a statistical study of "allergy in children" based on the comparison of 75 children with 75 adults, Rinkel[126] concludes that foods are not more important sensitizing factors in children than in adults. Another report using the statistical method is that of Bryce[127] on the relation of age and sex to incidence and prognosis in quinine hypersensitivity. In last year's review the opinion was expressed that the small nonuniform populations seen clinically are of doubtful value for statistical analysis.

In the present stage of our clinical knowledge, reports such as Lambright's[128] would seem valuable. This author discusses mistakes in allergic diagnosis and treatment with a series of short illustrative case histories. More instances of honest confession where the assumption of allergy is shown to be false would have a salutary effect.

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American Academy of Pediatrics

Proceedings

ANNUAL MEETING OF REGION I OF THE AMERICAN ACADEMY OF PEDIATRICS

THE annual meeting of Region I of the American Academy of Pediatrics was held on Nov. 11 and 12, 1938, at the Strong Memorial Hospital, School of Medicine and Dentistry of the University of Rochester, at Rochester, N. Y. Every state and province in the region was represented. Dr. Guilbeault, of Montreal, the first French Canadian pediatrician to be a Fellow of the Academy, was present.

The meetings were opened by Dr. Allan Valentine, president of the University of Rochester. At the meeting of the state chairmen, Dr. Martha Eliot, Dr. Doris Murray, and Dr. Lucy Bierman were present as representatives of the Children's Bureau in Washington. Dr. Grulee, secretary of the Academy, was present.

A feature of the meeting was a radio talk by Dr. Beaven on the work and influence of the Academy and its relationship to child health. Dr. Grulee also talked on the dangers of contracting infection in children, with special reference of its application in the home and in the school.

It was agreed that the next meeting of Region I would be held in New York City in June, 1939.

Nominations were approved for associate chairmen of Region I, Dr. Lewis Webb Hill and Dr. Warren R. Sisson of Boston. These nominations were referred to the Executive Board of the Academy.

The following resolution, presented by Dr. A. D. Kaiser, was passed:

"RESOLVED: In view of the well-established fact that the child with cardiac disease is a cripple in every sense of the word, it is the consensus of opinion of the assembled pediatricians of Region I of the Academy of Pediatrics that the cardiac cripple should be given medical, hospital, and convalescent care by the state agency responsible for the program of services to crippled children."

The meeting of state chairmen was held at the Strong Memorial Hospital, Rochester, N. Y., Nov. 11, 1938, Dr. Stanley H. Nichols, chairman. Those present were: Dr. Clifford G. Grulee, secretary and treasurer, American Academy of Pediatrics; Dr. Oliver Stringfield, Connecticut; Dr. Harry H. Donnally, District of Columbia; Dr. Thomas A. Foster, Maine; Dr. Colin Stewart, New Hampshire; Dr. LeRoy Wilkes, New Jersey; Dr. Alexander T. Martin, New York; Dr. Paul W. Beaven, New York; Dr. Joseph Stokes, Jr., Pennsylvania; Dr. W. P. Buffam, Rhode Island; Dr. Alton Goldbloom, Quebec; Dr. Martha Eliot, Dr. Jessie Bierman, and Dr. Doris Murray, Children's Bureau, Washington, D. C.

A motion submitted by Dr. Kaiser was passed and referred to the general meeting of Region I. This resolution was put before the full session in the afternoon and was unanimously indorsed.

Dr. Lewis Webb Hill, of Boston, and Dr. Warren R. Sisson, of Boston, were approved as associate regional chairmen of Region I.

The state chairmen voted to hold the next meeting of Region I in the spring of 1939 in New York City, and after Dr. Donally read the invitation, to hold the 1940 meeting of Region I in Washington, D. C.

Dr. Nichols.—Some of the state chairmen were not able to attend the annual meeting in California. In our report from this region we had some general reports

and all the state chairmen's reports. Since there was not space enough in the JOURNAL to print them all, many of you have not had all the reports. We shall have those sent to you.

In the report of Region I there were three points I would like to present: First, the object of the Academy as stated in the Constitution reads: "The object of the Academy shall be to foster and stimulate interest in pediatrics and correlate all aspects of the work for the welfare of children which properly come within the scope of pediatrics."

Second, that we should coordinate child health services in each state and province; that it is clear that all our state groups have realized the importance of coordinating and stimulating the existing official and nonofficial agencies dealing with child health and the promotion of pediatric knowledge among pediatrists, general prac titioners, and the public groups.

Third, the most important single activity of any state Academy Fellowship is to act as the stimulating, coordinating keystone of child health development for both the state medical society and the state department of health. This is fully realized by our state chairmen. Most of the other important activities of the Academy can be based on these three points.

This, as I see it, is our vital problem at the moment. These recommendations will be sent to you with the state reports.

Dr. Eliot will talk to us about the extension of child health programs in Region I if new funds become available in the future and how the state chairmen can be of service. Later the state chairmen may wish to present something from their own states or to ask questions.

Dr. Martha Eliot.—When Dr. Nichols asked me to discuss what the future holds, I began to wonder what I could say because I really do not know what the future holds. I can review what has happened in the past three years in certain respects, and I may bring out a few developments which are significant and which indicate the trend of the lines along which the child health program will develop. Any development will be gradual. There will not be anything which will be a sudden pouring down, a huge program which must be developed all at once. As far as the child health program is concerned, I assume it will be an expansion of the work already underway under Title V of the Social Security Act. That means the program will still be in the hands of the states, not a federal program superimposed upon the states. The states will continue to prepare and submit plans. The responsibility of the federal government will continue to be that of approving plans under conditions set up by Congress in any amendments they may see fit to make to Title V.

Certainly the general view expressed at the National Conference, that the function of the federal government is to offer financial and technical advice to the states in developing their own programs, will still hold throughout anything that may develop. That is basic.

In the last three years, during which we have had some real experience with the program in all the states, it has been evident that the medical contribution has come through different channels. In the first place, there has been a very definite contribution through the advisory committees that have been appointed—not the contribution that it might be, however. I am fully cognizant of the fact that the advisory committees that have been appointed by the state divisions of maternal and child health have not always functioned well. Where the blame rests is not always clear, but there is an opportunity for a lot more to be done.

It seems to me there should be developed in the child health field, as in the crippled children's field, more so-called technical committees of experts to advise. In the crippled children's program many states have now what they call a technical committee, made up of half a dozen orthopedic surgeons, and in thirteen areas a

pediatrician is a member of that committee. There should be, of course, a pediatrician on that committee.

The child health programs have not gone quite as fair in the development of a group of technicians. By that I mean experts in pediatrics who can advise the maternal and child health division with regard to the technical phases of the health program. That is one point I want to make.

The development, of course, of child health conferences has been varied in different states. Some states have not wanted to have any child health conferences. There are only a few of those. Most states have developed child health conferences, and in more than thirty states the physicians who are conducting those conferences in rural areas and smaller towns (in thirty-three states) are paid for those conferences. There are more than three thousand physicians now being paid for that particular type of service in rural areas. That is entirely a new development in the last three years.

However, only seven hundred rural counties have child health conferences, and, since that is about one-third of the rural territory, we have quite a way to go in that field.

When I spoke of more than three thousand physicians being paid, I did not mean that that is the total number of physicians taking part. Many are volunteering services.

The third thing is the development of the consultation service. There are two types of consultants who have been employed by the state health departments. One is the so-called administrative consultant—a specialist either in obstetrics or pediatrics who helps develop the administrative program in the state. In thirty of our states the director of the division is a pediatrician; five states have obstetricians; and the rest of them have persons who have experience along child health or general public health lines. The administrative consultant goes about from town to town and county to county, helping develop the administrative aspects of the program.

Then, on the other hand, there is what we might call the case consultant, who is a clinician, who in a number of states in a given area is offering consulting service to general practitioners in the fields of obstetrics and pediatrics. The plans developed in the various states with reference to that consultant work differ in a considerable degree. Twenty-two states are employing obstetricians and pediatricians to serve an area full or part time, on a salary basis, to act as a case consultant to help improve the quality of the care given in a particular area. On the other hand, about twenty-three states are employing case consultants on a case basis, not on a full-time basis or even a half-time basis. Some of the states that you represent are doing that.

I would say that it is very good that the states are doing this in different ways, because we shall discover the effect of this type of service through the diversity of the program.

It seems to me that, if the program expands, there will be need for more such work, especially from the point of view of both the physicians who conduct the conferences and the physicians who are giving technical specialty consultation advice to general practitioners in areas where there is none of this, and in families who, of course, are not able to provide their own consultant service.

I am not going to go into a discussion of postgraduate education because that is very familiar to you. I want to point out, however, that there seems to be an increasing demand for postgraduate medical work in centers throughout the country. I have had one pediatrician consult me at length in regard to the development of postgraduate service in connection with a medical school. It seems to me that is something the future holds in our teaching field.

You may be interested to go back to the group of doctors in rural areas who are being paid for their work in the child health conferences. This year I think

nearly $350,000 is being budgeted by the states for that particular purpose. We asked the states to tell us what they thought their needs were for this current year and, if they knew, to specify the cost. We were trying to get some idea what the state health departments were thinking about. They submitted some interesting material. Twenty-eight states submitted material with actual cost data attached, and all of the needs were along the lines they had already tried and found reasonably good and they wanted to expand.

Twenty-eight states sent in requests showing that they need twenty-two million dollars annually. Of that, fourteen million dollars was for public health nurses. With that money they would be able to cover a thousand counties which have no nurses now, and they would be able to add nurses in other counties from areas where more are needed. That is, only twenty-eight states that expressed this need. As we reviewed them state by state, these requests seemed very reasonable to us.

The second largest item of that twenty-two million dollars was medical services which they say need to be rendered and for which there is no provision. Part of that would be for services in child health and professional conferences, part of it for payment to physicians to give medical service to families who are unable to get it now.

That just corroborates what we have been saying right along for these three years—that there is very great need for those medical services to supplement, support, and make the health service efficient. There is not much use in examining children in a child health conference if you do nothing about the defects that are found. That is becoming more and more apparent.

Obviously the problem of quality of care and service is the thing which must be uppermost in our minds if there is going to be expansion of the program. If we do not manage to provide quality of care, we might as well not expand the service. It seems to me there is something we all must bear in mind. It is something to which the pediatricians of the country can make a very great contribution: that is, working out plans in the states for qualified service regardless of what the type of service is.

We need to have highly qualified administrative consultants in these states, highly qualified case consultants, and we need better and better qualified local general practitioners who will be doing much of the child health work in the local communities.

The only way we can get better work done by the local practicing physicians is by providing them with consulting service so that they have the facilities to call on and by giving them an opportunity perhaps to come back from time to time to some medical center for some additional work.

There are, it seems to me, several devices for the establishment and maintenance of quality. It is extraordinarily important. I have spoken of these technical committees. Those committees might be state-wide in a state with a small population. In states like this and the others in the northeast, I think it is possible that there would have to be either representatives or local technical committees in regions to advise and help the local health administrative officer, because the administrative officers are going to need the advice of the most skilled physicians in their communities. Whether it should be on state-wide, regional, or county basis would depend entirely on the state.

I have spoken of these two types of consultants. I would like also to say one word with regard to the development of demonstration child health conferences to which the general practitioner in the local community who wants to run a conference but does not know how—has never seen one—can go and learn how to do it through observation of a going concern, one which is set up in as ideal a fashion as possible. I think Connecticut and one or two other states have developed that form of teaching program.

We are going to expect general practitioners to do many things they never had any thought of doing before. If they are taught through observation and actual practice, we shall get much farther in the program.

This is not quite so applicable to this region, perhaps, but there are areas where diagnostic clinic centers are needed. In other parts of the country there are wide territories where good diagnostic centers are needed desperately, because there is no place where the general practitioner can get laboratory, x-ray, and other services he needs for a diagnosis, or where he can get consultation. If funds are increased there will be opportunity to provide for the use of general practitioners, and of course for the people and the children, these diagnostic centers where accurate diagnoses can be made.

Dr. Buffam.—I would like to ask what is the ideal supervisor of child hygiene for a state. Should he be a public health man or a man who has been a practicing pediatrician?

Dr. Eliot.—Of course there are different opinions, but this is the opinion of the state health officers in conference three years ago. They declared in a statement accepted by the whole conference of state health officers that the ideal director should be, first and foremost, a person who is trained clinically in obstetrics or pediatrics or both, if possible; second, someone who has had some experience in child health work; and third, if possible, a person who has had academic training in public health, but the academic training to be superimposed on the clinical training, which is the basic thing.

Dr. Buffam.—I suppose it would be difficult to get an expert pediatrician who has a public health degree, too.

Dr. Eliot.—Out of fifty, thirty have had public health work. Thirty are pediatricians, five obstetricians, and nine have been in child health administrative work, mostly people who have been in their jobs for a long time. Of the new people in the field in the last three years, I think almost every one has had basic pediatric or obstetric training. I think there has been only one appointment in the last three years in which that is not true. The state health officers themselves agreed that that was what they wanted, and they have really come very close to it.

Dr. Foster.—I would like to ask about the interpretation of Title V. It emphasizes the work in the rural communities, and then it says "and in such cities that need help in certain areas." Has that been interpreted to cover child health conferences or well baby clinics in cities?

Dr. Eliot.—If a city of moderate size has demonstrated to the state health department that for certain areas of economic distress they needed help, there is no reason why that should not be worked out. By and large, of course, the states, knowing their enormous rural needs, have concentrated on rural areas, and I think, rightly so. In a city it is easier to get a group of citizens to support a baby conference. In the rural areas it is harder to do that. There has been nothing in the Act that would prevent work in cities—there was one demonstration in New York City.

Dr. Nichols.—May I ask that we continue this story in our spring meeting; Dr. Eliot said to me she was particularly anxious to know of any states where the Academy has been of service in becoming the child health combination between the state medical society and the state department of health, and how that was done; or of places where plans were being made, what the plans are.

Dr. Eliot.—I would like to add one thing. The chairman may be interested to know that I am so interested in working out this relationship between what the professional people in the states and the state health departments are doing that I have asked Dr. Helmholz and Dr. Grulee into our Children's Bureau staff meeting next month, to sit with us for a whole day and to discuss the problems from the point of view of the state administration, how the state administration must get to

these people, and, on the other hand, how you can get to the state departments. I hope that something may come out of that session. Also, Dr. Phillip Williams from Philadelphia is coming at the same time, so that we can have a group meeting within our own Children's Bureau circle to try to discover what we can do to further that part of the work.

Abstracts of the papers presented follow:

Vitamin A Content of the Blood in Fever

S. W. Clausen, M.D., F.A.A.P.*

The concentration of vitamin A in the plasma was determined by a modification of the Price-Carr reaction with antimony trichloride. Significantly lower values were found during infection. The decrease was proportional to the severity and duration of the infection. Several days after the temperature had returned to normal, the amount of vitamin A in the plasma rose above normal. Artificial hyperthermia also caused a marked fall in the vitamin A of the blood, followed by a rise above normal. Experiments with animals showed that infection and artificial hyperthermia increased the rate of disappearance of vitamin A from the tissues. During infection the ingestion of vitamin A or of carotene was not followed by a normal rise of these substances in the blood.

These observations show that low values for vitamin A of the plasma do not indicate a corresponding decrease in the stores. They show how mild symptoms of vitamin A deficiency may occur during infection and suggest the desirability of diets rich in vitamin A during convalescence from infection.

Visual Adaptation as Tested With the Biophotometer and the Vitamin A Content of the Blood

W. S. Baum, M.D., and Augusta B. McCoord, Ph.D.

Ninety-eight children were tested once with the biophotometer. When the standards supplied by the makers of the apparatus were used, the dark adaptation of 33 of the children was normal, while there were 64 children in the intermediate group and 1 in the subnormal group. If the more rigid standards recommended by Jeans were used, 32 subjects were in the normal group, 47 in the intermediate group, and 19 in the subnormal group. These last results are in agreement with those reported by Jeans. There was no correlation between the vitamin A and carotene content of the blood and the biophotometer readings.

Nineteen subjects were tested until constant readings were obtained with the biophotometer. Under these conditions, the scorings of the children were much improved. There was a slight correlation between the carotene or pro-vitamin A content of the blood and the biophotometer readings of this group.

The vitamin A absorption test was given to 10 trained subjects. Six subjects with normal vitamin A absorption showed a transitory improvement in dark adaptation which coincided approximately with the peak of the vitamin A content of the blood. The dark adaptation of four subjects with subnormal vitamin A absorption curves showed improvement which persisted for twenty-four hours. These results were not absolutely definite but were suggestive.

Vitamin A Absorption Tests in Celiac Disease and Nonceliac Disease

B. B. Breese, M.D.

Celiac disease is characterized by failure to absorb and digest properly carbohydrates and fats. Besides the clinical picture, which is well known, certain laboratory findings are considered characteristic of the disease, namely, a high percentage of fat in the stools and a flat glucose tolerance curve.

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*Speakers are all from Rochester, N. Y.

Vitamin A is a fat-soluble vitamin, and it would be expected that in celiac disease this vitamin would not be well absorbed. To test this hypothesis a series of vitamin A absorption tests were done on patients with celiac disease and in patients without celiac disease.

The patient was given a highly potent preparation of haliver oil with a known vitamin A content, and determinations of the Vitamin A content of the blood are made before and after the administration of this oil by mouth.

In normal individuals or in patients with other conditions besides celiac disease, there is a marked rise in the vitamin A content of the blood, reaching the maximum at about four hours after administration and gradually declining to the fasting level within twenty-four to forty-eight hours. In celiac disease, although there may be some rise in the vitamin A content of the blood, this rise is very slight. The fasting level of xanthophyll and carotene (the plant pigments of the blood) is also below that of patients without celiac disease.

This test of vitamin A absorption is considered to be of value in the diagnosis of celiac disease.

Distribution of Vitamin A in the Body Tissues of Experimental Animals

Augusta B. McCoord, Ph.D.

Different animals vary in their capacity to store vitamin A. After the administration of a massive dose of vitamin A, the recovery of the vitamin in the liver of the rat was eight times as great as that in the liver of the guinea pig. When excessive amounts of vitamin A were given to the guinea pig, large quantities of the substance were present in the large intestine and in the skin.

Massive doses of vitamin A were given to two groups of vitamin A deficient rats. A study of the vitamin A content of the tissues one day and eight days after the administration of the vitamin showed that there was a slight decrease in the liver, brain, and testes; an actual increase in the eye; and a rapid decrease in other tissues.

Recovery of vitamin A was definitely low in the livers and lungs of rats which succumbed to the infection of *B. paratyphosus muris*. The marked increase noted in the vitamin A content of the adrenal glands seemed to indicate that vitamin A was actually mobilized, probably from the liver, and transported to the adrenal glands. There was a definite lowering of vitamin A in the liver, lungs, and adrenal glands of rats due to hyperthermia.

The Value of Urea Clearance Tests in the Prognosis of Chronic Nephritis

Frederick S. Gachet, M.D.

Renal function, as measured by the urea clearance test, is often greatly reduced in acute nephritis in childhood. The level to which it may be reduced, and yet later return to normal, is lower than the level commonly accepted for adults. Unusual delay in the recovery of good renal function indicates that recovery may be incomplete and chronic nephritis may result.

This test is a useful one for following the progress of chronic nephritis in childhood. It is one of the most dependable means available for the differentiation of nephritis with edema from nephrosis.

Data are presented concerning the "augmentation limit" in childhood.

Prognosis of Chronic Glomerular Nephritis in Children

Albert W. Snoke, M.D.

A comparison of a study of the prognosis of glomerular nephritis in children in Rochester, N. Y., with a similar study made in San Francisco, Calif., demonstrates a less severe prognosis in the Rochester area.

Some Aspects of Experimental Leucemia

G. Burroughs Mider, M.D., and John J. Morton, M.D.

Lymphomatosis occurs frequently among mice of the dilute brown strain when they are 650 to 800 days old. Forty-eight of sixty mice that were painted with methylcholanthrene in benzene developed leucoses and died before the 250th day of life. Three types of reaction were found:

1. General lymphomatosis characterized by lymphadenopathy, with infiltration of the liver, spleen and bone marrow, and sometimes a leucemic blood picture.

2. Mediastinal lymphoma without alteration of the liver, spleen, lymph nodes, bone marrow, or blood.

3. Myelopoiesis.

A comparable effect was not obtained by painting dilute brown mice with benzene alone.

Absorption and Excretion of Iron in Normal and Anemic Dogs Under Experimental Conditions

Paul F. Hahn, Ph.D.

Experimental use of radioactive iron shows that the normal dog does not absorb appreciable amounts of iron when the salts are fed in amounts corresponding to several times that present in foodstuffs. In contrast, the anemic animal with a demonstrated deficiency of iron takes up considerable amounts of the metal. Following a single feeding of radioactive iron to an anemic dog, absorption is indicated by the rapid appearance of the element in the plasma. The amount present in this blood fraction increases gradually until about the twelfth hour. By the end of twenty-four hours there is no longer any evidence of its presence here. This also demonstrates that the plasma is an important vehicle for the transport of iron.

Some of the new iron is found combined with protein in the red blood cells four hours after feeding. In twelve hours one-third of all the iron which ultimately finds its way into new hemoglobin is already in the red blood cell in some undetermined form.

Preliminary studies indicate that excretion of iron in the urine is almost negligible. The amount excreted by the gastrointestinal tract is much less than has been supposed in the past. These findings are in harmony with those mentioned above. Where there is no need for iron, it is not absorbed in appreciable quantities, and the demand for excretion is obviated. Where there is a real need, as in anemia, the iron is absorbed, and, since it is utilized for hemoglobin formation, there is likewise no excretory requirement.

Case of Pericarditis of Unrecognized Etiology

Edwin R. Reynold, M.D.

A four-year-old child, who was underdeveloped from an insufficient diet, was sent to the hospital with the symptoms of general edema and severe dyspnea. Urinalysis suggested nephritis, but other laboratory findings did not support this diagnosis. The x-ray film showed an enormous heart shadow due largely to pericardial effusion. Other organs showed passive congestion. No evidence was found pointing definitely to any focus of infection. With symptomatic treatment, including vitamin B_1, the child recovered and was discharged on the twenty-first day.

With the similarity of symptoms in the case presented to the symptoms in reported cases of vitamin B_1 deficiency, I have concluded that the condition resulted from an avitaminosis, and that the edema and the symptoms found in the various organs were caused by the cardiovascular disturbance.

Familial Cerebral Sclerosis (Pelizaeus-Merzbacher Type) (With Presentation of Three Cases)

John Aikman, M.D., F.A.A.P.

Three sisters, aged 14, 17 and 24 years, have never been able to walk. They were normal at birth. In all three, the trouble was first noticed at about one year. Spasticity of the legs is marked, and while the arms are not normal, the girls are able to feed themselves. They move about the house and even up the stairs on their hands and knees, the latter being heavily calloused. They have never been able to talk well but have "a language of their own" which the parents can understand. They show rotatory nystagmus and a coarse tremor. Mental impairment is marked, but they can see and hear. There is no loss of control of either the bowels or bladder.

The course of the disease has been slow but progressive. The parents state that no other cases have ever occurred in any relatives; this may not be true because they have not appeared very cooperative in fact finding.

While the symptoms are not exactly like those of any of the heredofamilial degenerative diseases, the cases fit best into the Pelizaeus-Merzbacher type of cerebral sclerosis.

Tuberous Sclerosis: A Report of Two Cases

Fred W. Bush, M.D., F.A.A.P.

Tuberous sclerosis is a condition found more commonly in the European races. The usual symptom complex is adenoma sebaceum, epilepsy, and mental deficiency. These are associated with tuberous tumors of the brain which tend to calcification. Because of the rarity of the condition, the two following cases are reported.

The first case was a normal female child until the age of 10½ years. At this time she developed a hemiplegia. The presence of adenoma sebaceum and a ventriculogram determined the diagnosis. Autopsy showed numerous calcified tumors.

The second case, a girl age 11½ years, showed the usual signs and symptoms. Roentgenogram of the skull, showing the presence of calcified brain areas, confirmed the diagnosis.

A Case of Precocious Somatic and Sexual Development in an Infant

Michael J. Gerbasi, M.D.

A twenty-four-month-old boy is presented showing premature sexual development, increased body size for the age, and greatly advanced epiphyseal growth. Repeated examinations have failed to indicate any intracranial involvement, such as pineal or pituitary tumor.

Primary Carcinoma of the Liver in a Six-Year-Old Girl

David Wolin, M.D., F.A.A.P.

A white girl, six years of age, was admitted to the Highland Hospital because of sudden, profuse and alarming hematemesis. The patient seemed well except for eczema until two months before, when she first complained of abdominal pains. It was then that the spleen was found to be enlarged for the first time and the hemoglobin 78 per cent (Sahli). The patient had three gastric hemorrhages before admission to the hospital and two after admission. She also passed blood by rectum for four days, and the stools were positive for occult blood for a long time. There was no evidence of icterus; the heart and lungs were normal; the abdomen was flat; the spleen was palpable two fingerbreadths below the costal margin; the liver was not

palpable; there was no demonstrable ascites or edema. Blood count showed evidence of a severe anemia. On the eighth day after admission there was marked evidence of peripheral edema, on the eleventh day abdominal distention, on the twelfth day dullness in both flanks, on the fourteenth day paracentesis of the abdomen yielded 860 c.c. of clear ascitic fluid. Two weeks after admission the patient passed soft foamy stools, from which the *Monilia psilosis* was isolated in almost pure culture. Five weeks after admission the left lobe of the liver became palpable; the veins of the thoracic abdominal walls became dilated and visible; and rapidly accumulating ascites became a prominent feature from then on.

Exploratory operation was performed two months after admission, with biopsy of the left lobe of the liver and splenectomy. The patient recovered from the operation and lived nearly five months after it. Report of biopsy was primary carcinoma of the liver.

A Case of Severe Staphylococcal Infection Treated with Staphylococcal Antitoxin

John Lichtz, M.D., and Wm. A. MacColl, M.D.

The patient, a seven-month-old female infant, developed a severe staphylococcal cellulitis of the back and anterior abdominal wall. The treatment consisted of supportive measures, transfusions, multiple incision and drainage, and 40,000 units of staphylococcal antitoxin. It is our impression that the antitoxin aided materially in the patient's recovery.

Three Cases of Amyotonia Congenita

Jerome Glaser, M.D., F.A.A.P.

A motion picture film shows the clinical characteristics of the disease as illustrated by three infants of different ages.

Studies Relating to the Value of Smallpox Vaccination With Culture Virus

Donald D. Posson, M.D.

A series of patients were vaccinated against smallpox with the chick embryo culture virus prepared by Rivers, with resultant takes. Two years later a number of these persons were revaccinated by use of the usual calf virus with resultant accelerated takes in a large percentage of the cases.

Experimental Infection in the Mouse Produced by Intranasal Inoculation With H. Pertussis

W. L. Bradford, M.D., and Mary Wold, A.B.

White mice were inoculated intranasally with a suspension of Phase I *Hemophilus pertussis*. They consistently developed interstitial pneumonia which was in all probability due to *H. pertussis* since the cultures from the lungs were usually pure.

This type of experimental disease was used to test the protective action of various immunizing agents. Criteria for measuring the degree of protection were (a) mortality, (b) bacteriologic cultures of the lungs and spleen, and (c) degree of pneumonic involvement of the lung. It was found that immune rabbit serum and hyperimmune human serum were protective when given simultaneously with the infecting organism. Mice immunized actively with *H. pertussis* vaccine were not protected when infected three weeks or three months after immunization.

Moving Picture Demonstration of the Circulation Within the Mesentery of the Rabbit

Stafford L. Warren, M.D., and Roger Harvey, M.D.

Illustrations in color were shown of the circulation of blood and serum in the smaller vessels and capillaries; the movement of the fixed tissue cells in the reticulum outside the vessel; the mobilization of leucocytes at sites of trauma; sticky endothelium; small foci of hemorrhage without clotting; platelets in eddies, plasma streaming; distribution of fat as sausage-shaped masses and finally spheroids; relation of capillaries to fat cells; discussion of capillary bed and dilation of precapillaries and arterioles and venules; the possibilities of fluid exchange.

Congenital Intestinal Abnormalities in Infants

T. Banford Jones, M.D.

Congenital intestinal abnormalities occur most frequently in the rectum and the region of the duodenum. They consist of atresial stenosis and abnormalities of intestinal rotation.

The most outstanding feature of the higher obstructions is the onset of persistent vomiting within 24 to 48 hours after birth. It occurs almost invariably at a definite time interval after feeding and soon becomes projectile in type. Blood in the vomitus is almost pathognomonic.

Various grades of abnormal distention (localized or generalized) and visible peristalsis are most constant findings.

X-ray examination should be done in every case. The flat abdominal plate will give valuable information. Subsequent examination after the ingestion of barium should be done.

The treatment of these abnormalities is surgical, and all patients should be given the opportunity of cure which only surgery offers. The closest cooperation between the pediatrician and surgeon is essential. The best of preoperative preparation and postoperative care on the part of the pediatrician is indispensable. This plus careful, meticulous surgery will lower the mortality rate which in our experience of about 35 patients is 25 to 20 per cent.

Early Adolescent Menstrual Difficulties

Willard M. Allen, M.D.

Disorders of menstruation occurring during early adolescence are usually mild and require no treatment. This is especially true of irregularity of the menstrual periods. Bimonthly bleeding also requires no specific treatment unless the blood loss is sufficient to interfere with health. These disorders should be considered as normal variations since they occur in a considerable portion of adolescent girls. Continuous vaginal bleeding, on the other hand, is one of the less common disorders, one which often may be severe enough to interfere seriously with health. This may or may not be associated with hyperplasia of the endometrium. It usually is associated with failure of ovulation and consequently with lack of the corpus luteum hormone, progesterone. Many of these cases are satisfactorily treated with progesterone, or with the closely related hormone, testosterone. These hormones should be given thorough trial before resorting to such drastic procedures as irradiation of the ovaries or hysterectomy.

Vascular Birthmark in Infancy: Diagnosis and Treatment

Forrest Young, M.D.

Hemangioma is the most common tumor of childhood. In most instances it is present at birth. It may occur in any tissue or location but most commonly occurs in the skin and subcutaneous tissues of the face.

Pathologically and clinically there are three different types; the capillary nevus or port-wine stain, the hypertrophic endothelial, or strawberry, growth, and the cavernous hemangioma. Any one lesion may have characteristic areas of all three types.

There is no very satisfactory treatment for the port-wine mark. The hypertrophic endothelial growths on the trunk and extremities should be excised; radium applications are most useful if they are on the face or are large and involving features. The cavernous type may occasionally be eradicated by injection of sclerosing solutions. All types, if extensive, may need surgical repair at a later date.

Head Injuries in Children

Fred W. Geib, M.D.

Mild and severe head injuries in children are commonly accompanied with symptoms of shock. The treatment of shock with subsequent bed rest is the most important and usually the only treatment needed in the vast majority of cases.

Children convalesce more rapidly than adults and as a rule do not have a permanent period of headache, dizziness, and psychic disturbances.

X-ray plates of the skull are not needed in most cases because they do not tell us the extent or degree of brain trauma.

Experimental Agranulocytosis

John S. Lawrence, M.D.

A disease has been found in the cat which is characterized by marked neutropenia and leucopenia. It is readily transmissible and has been carried through thirteen transfers. Berkefeld V filtrates from the liver and from washings from the upper respiratory tract and lung tissue have been shown to be active in transmission of the disease. The incubation period is from six to eight days.

The Inactivation of Staphylococcal Toxin in Vitro by Sulfanilamide

C. M. Carpenter, M.D., G. M. Barbour, and P. L. Hawley

Staphylococcal toxin was inactivated by exposure to sulfanilamide in vitro. This was demonstrated by the survival of 89 per cent of 400 mice injected intraperitoneally with the sulfanilamide-toxin mixture and death of all of the 100 controls which had received the toxin only. It was observed that 15 mg. of sulfanilamide per minimal lethal dose gave as complete inactivation as 20 and 30 mg., but that smaller amounts resulted in decreasing degrees of inactivation.

TABLE I

INACTIVATION OF STAPHYLOCOCCAL TOXIN WITH SULFANILAMIDE

GROUP	MG. SULFANILAMIDE MIXED WITH 1 M.L.D. OF TOXIN	MICE INJECTED WITH TOXIN-SULFANILAMIDE MIXTURE			MICE INJECTED WITH TOXIN ONLY		
		NUMBER INJECTED	NUMBER SURVIVED	PER CENT SURVIVED	NUMBER INJECTED	NUMBER SURVIVED	PER CENT SURVIVED
1	30	120	107	89.2	30	0	0.0
2	20	180	160	88.9	45	0	0.0
3	15	100	89	89.0	25	0	0.0
4	10	100	68	68.0	25	0	0.0
5	5	60	36	60.0	15	0	0.0
6	3	60	19	31.7	15	0	0.0

Vitamin C Studies in Rheumatic Fever in Children

Albert D. Kaiser, M.D., F.A.A.P., and Estelle Hawley, Ph.D.

A number of studies dealing with the behavior of vitamin C in rheumatic individuals has been reviewed. The basic vitamin C level of whole blood has been

studied in nearly one hundred rheumatic children and similar observations were made in children without known disease. The difference in these levels has been recorded. The response to large doses of vitamin C in these two groups has been noted. It was found that the rheumatic group responds poorly to larger doses of vitamin C compared with the normal children. This suggests increased utilization of vitamin C in rheumatic subjects. The relationship of the incidence of streptococci found in the tonsils to the vitamin C level found in the blood and in the tonsillar tissue was determined. It was found that hemolytic streptococci occurred five times as often in the tonsils of children with low vitamin C values as compared with those that had adequate amounts of vitamin C in the blood.

MEETING OF STATE CHAIRMEN OF REGION III

The state chairmen of Region III met on Friday, October 29, 1938, at the Hotel Statler, Detroit, Mich., at the time of the meeting of Region III. The following men were present: Henry Helmholz, Clifford G. Grulee, A. Graeme Mitchell, Edgar E. Martmer, Franklin P. Gengenbach, Colorado; George Munns, Illinois; Roger Kennedy, Minnesota; Ralph E. Pray, North Dakota; Goldie Zimmerman, South Dakota; E. G. Padfield, Kansas; Matthew Winters, Indiana; Lee Forrest Hill, Iowa; Abraham Schwartz, Wisconsin; Henry E. Utter, Rhode Island; Warren Sisson, Massachusetts; and W. C. C. Cole, Michigan.

The first order of business was the consideration of applications for membership.

Because the annual meeting of the Academy is to be held at Cincinnati in the fall of 1939, it was decided not to have a meeting of Region III in the spring of 1939.

A meeting of state chairmen of Region III will be held in May, 1939, to carry on the business of the region. The exact date of this meeting will be set by the regional chairman.

It was decided to have a business session at the next meeting of Region III. At this meeting open discussion of business as well as the initiation of new business from the floor will be encouraged.

The discussion included publicity for the Academy, the relations of the Academy with state departments of health and the federal government under the Social Security Act, and the report of the Committee on Contact Infection. Dr. Lee Forrest Hill discussed the work of this committee covering the children's camps. He also spoke concerning the cooperation with the P. T. A. as well as the problem of nursery school supervision. In addition, the matter of adoption was discussed.

It was recommended that each state have regular meetings of the members to consider both regional and local problems and to enable the members to take a more active part in the affairs of the Academy.

EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DEL MONTE, CALIF., JUNE 9, 1938

Round Table Discussion on Dental Caries
The Disease and Its Significance as an Indication of Nutritional Adjustment

Chairman: Harold J. Noyes, D.D.S., M.D., Chicago, Ill.
Assistant: Harold F. Hawkins, D.D.S., San Francisco, Calif.

CHAIRMAN NOYES.—Dental caries or decay of the teeth is one of the most common and annoying disturbances of civilized man. While a complete and satisfactory explanation of the disease is still lacking, a great deal has been learned about it. We are no longer justified in assuming an attitude of complete ignorance of its causes and treatment.

If we summarize our knowledge of dental decay in the same way as we do other diseases, we are led to the impression that it is a bacterial disease: the lesions are caused by the acid produced by bacterial organisms lodged on the surfaces of the teeth: the circumstances which permit the growth of the bacteria are influenced by a great many conditions of which the diet of the patient is important. But in the same way that all persons do not react in identical fashion in behavior, they do not react in the same way with respect to the development of the contributory causes of dental decay. For this reason treatment must be adapted to the individual. At the present time no "cure all" has been discovered which will prevent the formation of cavities for every one.

It can be said conservatively, however, that more than 50 per cent of the cavities present in children's teeth could be prevented if we utilized the information which we now possess and could gain cooperation from the patient and parents necessary in making our advice effective.

It is also very interesting that the state of health which maintains a child free from dental caries often exerts a very beneficial effect upon growth, development, and resistance to disease. The number and nature of the cavities that occur in a child's teeth are often an excellent index of his nutritional adjustment.

In the interest of objective thinking I would like to present dental caries as a disease entity, recognizing that the furtherance of our investigations and the maturity of our thought may alter our classification to that of a syndrome. Just as in parliamentary procedure the presentation of a specific motion permits pointed discussion, so the presentation of this condition in the accepted academic form of a disease provides a basis for discussion which is often lacking when the entity itself is confused by consideration of factors contributing to these pathologic changes of the teeth.

Definition.—Dental Caries is a bacteriologic disease of the calcified tissues of the teeth. The particular organisms and the exact mechanism by which characteristic lesions are produced in typical locations are still matters of controversy. Once initiated they progress evenly or intermittently to the involvement of the dental pulp, or become spontaneously arrested in any period of their development.

INCIDENCE

Race.—While from examinations of the teeth from skeletal remains of aboriginal races, the disease appears to have been less common in ancient times, there are few, if any, adequate samples of human remains which fail to show its existence. Indeed, in some cultures of premodern periods it appears to have been almost as prevalent as in certain modern communities.[65] There are no contemporary races which are immune. The present racial differences appear to be more related to environmental conditions than racial characteristics.

Sex.—There is no appreciable difference in susceptibility between the sexes when the entire life span is considered.[16, 82] Certain constitutional differences, notably the more rapid adolescent change[22, 83, 93] and the period of pregnancy, provide intervals unique in the female which may temporarily alter this parity in the same way that environmental conditions imposed by a particular culture may affect either sex. There is no evidence that any sex-linked quality either predisposes to immunity or susceptibility.

Age.—The technique and criteria adopted by various investigators of age incidence of dental caries differ so widely that comparison of their findings is practically impossible. It may be said in general that the first two decades of life demonstrate an appreciably greater susceptibility to the disease. In this period the ages 5 to 6, 9 to 10, and the time of adolescence are notably prominent.[83] Following the twentieth year there is a gradual though uneven tapering through maturity, middle age, and senescence. There is no age when teeth are present that enjoys absolute immunity.

Socio-Economic Levels.—In general the privileged classes have a somewhat lower incidence than those in the low wage and indigent levels. Notable exception to this generality is the decreased susceptibility found in institutionalized groups where intelligent attention to dietary regimen and restriction of sweets prevails.[53, 75, 95]

Seasonal.—Recently there has appeared the only report upon seasonal variation of dental caries with which I am familiar.[25] This limited study, embracing 143 young adults residing in one locality, indicates a direct correlation with the hours of sunlight. While the susceptibility of the group varied during the two years of the investigation, the winter incidence doubled the summer, and the maximum and minimum peaks were attained in the same months (December, maximum, and June, minimum) both years. There were individuals maintaining immunity throughout the entire study as well as a small percentage who supplied a reciprocal curve.

ETIOLOGY

The etiology of dental caries has been unnecessarily complicated by the failure of investigators to differentiate between the active causative agent and the contributing environmental factors which affect the former. The rivalry between champions of local or constitutional causes, or the many subdivisions of both, has centered attention upon restricted analysis rather than comprehensive synthesis. This is somewhat surprising as analogous conditions exist with respect to other bacterial diseases without similar chaotic effect. For example, there is general agreement that constitutional factors may affect the susceptibility to tuberculosis without raising any question concerning the role of the tubercle bacillus as the active etiological agent of the disease.

Active Etiological Agent.—The evidence is preponderantly in favor of acidogenic bacteria as cause of carious lesions in the enamel. Whether this be limited to the lactobacillus, as some believe,[18, 51] or to other microorganisms producing acid[19, 29, 84, 101] or to the symbiotic action of combinations of organisms,[26] must be left for further investigation. The present state of our knowledge leaves little question that the lesions of caries of the teeth are due to three conditions: the generation of acid, the digestion of protein material, and the protection from oral fluids and

displacement of the bacterial entities. Carious lesions have never been demonstrated which, upon adequate inquiry, failed to reveal organisms possessing properties which fulfill this condition.

Contributory Etiological Factors.—Conditions favorable or antagonistic to the growth of these organisms, or organism, as the case may be, are dependent upon the regional and constitutional environment provided by the host. It would seem too obvious to require statement that in a given individual one or another of the environmental factors may determine the conditions which tend to prevent the activity of the active agent. The fact that these contributory factors may vary with the subject and that when many persons are studied they will fall into groups furnishing somewhat similar reactions, supplies evidence establishing the validity of the respective contributory factor. It is equally obvious that this evidence is in no way a contradiction of the existence of other contributing factors.

Certain of the more important contributing etiological factors are briefly suggested in the following paragraphs.

Diet is unquestionably an outstanding factor. It has been possible to both increase and curtail the disease by dietary regulation. Experiments upon institutionalized children by diverse investigators in widely separated locations have shown a surprising uniformity in that they appear to be able to limit the active caries in between 60 and 68 per cent of the children studied.[14, 17, 41, 53, 63, 75, 87] It should be recalled as well that in all instances some of these children were immune before dietary intervention, and some failed to respond to the imposed regimen. The elements in dietary supervision which appear to be most important include restriction of carbohydrate,[20, 53, 63, 66] adequate mineral,[1, 61] in quantity as well as proportion of calcium to phosphorus,[14, 58] vitamins D, B_1,[30, 74, 75] and C,[32, 33, 34, 40] adequate caloric requirement, and a balance in the aggregate assimilable food favoring an alkaline rather than an acid residue.[54, 66, 67, 68] In addition there is reason to believe that the physical, as well as the constituent qualities of the food, may exert some influence upon the mouth flora in the process of mastication. The variable reaction between individuals and in the same subject at variable times with respect to digestion, assimilation, and metabolism, as well as functional reaction, is responsible for the limited effect which the control of this factor can exert upon the aggregate of any group.

Heredity.—Dental caries is neither congenital nor hereditary. The so-called hereditary immunity or predisposition discussed in the literature refers to a diathesis. It is possible that the contributory factors, particularly metabolic function, salivary function, and tooth structure, may be strengthened or diminished through direct transmission from parent to child.[53, 67, 98] Yet dietary habits and other environmental influences which affect caries incidence are so frequently handed down from one generation to another that it is often impossible to accurately determine the exact significance of these factors. Certainly the absence of caries in people living under primitive conditions is not due to heredity. And there is very little evidence to indicate that an immunity possible of transmission can be acquired.

Saliva.—There is good reason to believe that the saliva is an important environmental factor. The controversy arises over the particular properties and constituents of the saliva which affects the various lesions. The principal items given consideration include the quantity and rate of flow, the hydrogen-ion concentration, the relative calcium and phosphorus content, the mucin, the ammonia-nitrogen, the carbon dioxide, and the amylase.[37] The action of the saliva may be either through the effect which it exerts upon the bacterial flora of the mouth or its ability to neutralize the acid produced by the active causative agent; perhaps both mechanisms operate. The obviously intimate relationship between the quantity and quality of the saliva and the systemic factors offers reasonable explanation for the correlations frequently

reported. Complete and satisfactory explanation of the exact manner by which the saliva affects the carious process and the systemic influence upon its volume and composition are still lacking.[6]

Tooth Structure.—The gross and minute anatomy of the teeth influence the morphology of the lesion and the site of attack. The quality of their calcification affects the rate and to some extent the direction of progress. In this manner certain teeth may offer greater or less opportunity for attack and may be different with respect to the rate at which they are destroyed.[11, 75]

The Dental Pulp.—It has been suggested that the dental pulp may affect the carious process by generation of fluid which when circulated through the dentinal tubules and diffused through the enamel inhibits the carious lesion.[11, 12, 59] This concept represents a hypothesis for which actual evidence of the operation of this mechanism is lacking. The contention of some that the tooth may be decalcified from within by diffusion of a decalcifying agent,[11] whether correct or false, cannot be considered as the same disease. An increase in the mineralization of the tooth in advance of the carious lesion frequently occurs, and it appears that this may be affected by the irritation of the portion of the dental pulp in proximity of the lesion.

Metabolism.—Metabolic changes, particularly with respect to the metabolism of minerals and carbohydrates, either through their effect upon the oral flora presumably through the saliva, or perhaps their action upon the dental pulp, supply another modifying influence upon the disease. It is probable that it is through this avenue so-called caries of pregnancy, lactation, and adolescence operate. There is no satisfactory evidence of the lowering of resistance of the tooth through removal of its mineral content. The delicate coordination between the rate and nature of mineral metabolism, the mineral requirement for bodily functions or their supply through the diet, may be altered sufficiently to affect susceptibility without distinguishable changes in the serum, calcium, and phosphorus of the blood.

Endocrine.—Metabolism is so intimately related to endocrine function that obviously the endocrine mechanism must be drawn into the picture.[14] The possible effects of endocrine disorders upon the numerous contributory factors to dental caries may be simultaneously beneficial to one and detrimental to another. As would be expected under these circumstances, no clear cut correlations have been established.[67]

Growth.—Growth is chiefly associated with both metabolism and endocrine function. It has been a common observation that periods of rapid growth presented greater hazards with respect to dental caries.[21, 46, 83, 93, 94] These appear to be proportional with the rate of growth. Nor does this seem illogical in the light of the effect which it might be expected to have upon the metabolic factor. The caries of adolescence is perhaps a case in point. The mineral demand for both increase in the skeletal framework and the energy requirement for adjustment often exceed the supply of the diet. If the mineral reserves are able to temporarily supply the deficiency, the oral environment may be altered in favor of bacterial growth responsible for caries. The tendency to crowd carbohydrates to supply quick energy further accentuates the condition through another contributory factor.

Systemic Disease.—As with endocrine disturbances the effect which systemic disease exerts upon dental caries depends upon the factors influenced and the direction of this effect. While no very satisfactory correlation has been established between caries of the teeth and any systemic disease entity, investigations demonstrate repeatedly that healthy children have less caries than those that are sickly, if we define health in the broad sense of reasonable attainment of their potentialities rather than the freedom from the gross manifestations of active disease.[83, 93, 94, 95]

Oral Hygiene.—It is unfortunate that commercial advertising and health propaganda convey the idea that careful regular cleaning of one's teeth by prophylaxis

by the dentist will insure freedom from decay. The statement that a clean tooth never decays is true only if clean is taken to mean absence of the responsible bacterial agents. Like all other contributing factors, care in brushing the teeth will be effective insofar as it inhibits the growth of the acidogenic organisms initiating the lesion. Dental hygiene must include consideration of all factors contributing to the disease.

PATHOLOGY

The pathologic changes in the hard dental tissues produced by this disease as in any other are determined by the action of the invading organisms, the gross and microscopic anatomy of the tissues attacked, and the reaction of the host. Moreover, they present a remarkably characteristic picture. These changes were accurately described by early investigators and have been later illustrated by excellent photographs of gross and microscopic specimens. The literature conveys the impression that more recent students of caries have overlooked these earlier studies or are consciously including lesions due to other causes, notably defects from imperfect formation of enamel and dentine and destruction of these tissues arising through unrelated etiology.

As the carious lesion is produced by bacterial products, the common sites of attack occur in protected areas. These may be roughly grouped under the heading of pit and fissure lesions (those originating in the crevices and pits of the occlusal surfaces of the teeth) and smooth surface lesions which are limited rather generally to the proximal surfaces and the gingival margins.

Pit and Fissure Caries.—In this type of caries the bacterial nidus obtains a foothold in the anatomic vantage points arising at the fusion of the borders of the calcification centers of the teeth. Influenced by the direction of the enamel rods this lesion diverges as it spreads toward the dento-enamel junction presenting a roughly conical form with its base inward and its apex at the crevice. As the more porous strata of dentine just below the enamel is reached, progress is more rapid, and the overlying portion of this tissue is both dissolved and undermined. With the removal of the enamel there is bacterial invasion of the dentine. Here, because of the widened surface of attack, the form is that of flame or cone-shaped area with base at the dento-enamel junction and the apex directed inward toward the dental pulp. In both tissues the region of destruction permitting the advance of the bacterial growth is preceded by a zone of partial decalcification. In the dentine (some believe also in the enamel) irritative stimuli transmitted along the dentinal tubules effect a defense mechanism through which there is activity of the odontoblasts producing a protective layer of secondary dentine and a sclerotic degeneration of the dentine between the advancing lesion and the new tissue.

Smooth Surface Caries.—The concentration and confinement of acid in smooth surface lesions is accomplished by the development of a bacterial plaque or beneath accumulation of food debris. The plaque furnishes the most favorable situation and frequently is extremely adherent to the tooth surface. The lesion in enamel presents a flamelike penetration toward the dento-enamel junction, the widest portion being at the tooth surface, the apex inward. In the same way, and for the same reasons, there is extension at the external strata of dentine, producing the characteristic changes described under pit and fissure. Thus in early stages of both enamel and dentine of smooth surface caries the lesions present cone-shaped zones with base externally and apex directed toward the central axis of the tooth.

The pathologic characteristics of dental caries are considered significant in the interest of avoiding confusion with other disease entities.

SYMPTOMATOLOGY

Objective.—It is often difficult to detect early caries in pits and fissures. With the progress of destruction the crevices are enlarged and the undermined area as-

sumes an unnatural appearance. While it is often difficult to observe early lesions on the approximating surfaces of the teeth, the zone of partially dissolved enamel may be detected by x-ray. Gingival caries is easily seen by the whitened appearance of the enamel beneath the plaque or upon removing food debris. When the enamel rods have fallen away, the roughening of the surface and later cavitation are easily detected.

Subjective.—If the carious process is gradual and the protective mechanism well developed, there may be extensive destruction before the patient experiences any discomfort. As might be expected, lesions that originate about the necks of the teeth are more often sensitive, for the enamel is thin and acid reaches the dentine more readily. Irritation of the pulp may be effected before secondary dentine and sclerosis offer protection. In early stages twinges of pain may be experienced through the stimuli of pressure, heat, hydrogen-ion concentration, and surface tension changes. Sustained and throbbing pain indicate inflammatory changes in the dental pulp. It is not always possible for the patient to accurately locate the origin of sensations.

DIAGNOSIS

The recognition of both objective and subjective symptoms has been the criteria of diagnosis in common practice. There have recently been developed methods of diagnosing caries susceptibility which permit recognition of a predisposing state prior to the development of lesions. The following represent methods which have been given sufficient clinical test to deserve attention.

Quantitative Estimate of Lactobacillus in the Saliva.—Lacto-bacillus counts from incubated samples of the patient's saliva are unquestionably of value. The variation of technique and culture media, as well as experience of the observer, furnishes difference in the reported significance of this test but in capable hands it has great value.

Smear Methods.—Another effective method is the examination of stained smears of scrapings from susceptible areas of tooth surfaces. Greater experience is required, both in the obtaining of samples and the reading of the smears, but the method has been demonstrated to have considerable merit.

Acidity of the Plaque.—Methods have been developed to test the acidity of the bacterial plaque, both by colorimetric indicators and use of the glass electrode. These tests have not been given the advantage of extensive use but show promise.

Salivary Analysis.—Satisfactory reports have been published of diagnosis from analysis of the calcium and phosphorus of the saliva together with estimations of its hydrogen-ion concentration. A relatively alkaline saliva with moderate calcium is mentioned as favorable, while a low phosphorus and high calcium with increasing acidity are detrimental. A low urinary loss of calcium and acidity of the urine has been reported to improve the outlook.

The ability of a salivary sample to dissolve calcium from powdered enamel has also been reported to be a practical test. The suspected caries susceptibility increases with the amount of calcium dissolved.

TREATMENT

Prophylactic.—The preventive treatment of caries has been centered about two principles: (1) The reduction of the caries producing organisms in the mouth and on tooth surfaces by mechanical measures, largely the brushing and scouring of the teeth, and less effectively by antibacterial agents; (2) the accomplishment of this end by controlling the contributory causes which affect the activity of the causative agent. Foremost in this category are the nutritional measures relating to both the oral bacterial flora and the tissues they attack.

Active.—The active treatment of caries is repair of the damage by dental restorations. This is preventive only in that each properly executed dental restoration removes a caries-susceptible area from the mouth. It does not in any way lessen the liability of other areas to attack.

Without radical changes in the dental curriculum the prevention of caries susceptibility through control of constitutional contributing causes must be considered as a medical problem, for the determination of appropriate measures requires the consideration of the body as a functional unit. Both dentists and physicians have been exceedingly slow to recognize and assume their appropriate positions in this cooperative relationship.

PROGNOSIS

Prognosis depends upon the ability of the dentist and physician to determine the contributing causes responsible and the degree to which they lie within their power to eradicate, the skill with which the damage is repaired, the age of the patient, and his cooperation.

DENTAL CARIES AND NUTRITIONAL ADJUSTMENT

Dental caries is a disease entity with a relatively clear-cut causative agent, which in turn is influenced by many environmental conditions. It is not a manifestation of any one functional activity as diabetes, for example. One would not expect to find absolute correlation between caries and any single contributing factor. The only absolute correlation will be with the active causative agent. Because of the manner and the degree to which other disorders affect the contributing factors, there will be relative correlation with many human disturbances.

As indicated previously, nutrition is an extremely important contributory factor. Also, the particularly significant features of nutrition related to dental caries lie in the carbohydrate and mineral metabolism and the acid-base balance of tissue fluids, recognizing that nutrition includes consideration of the foods offered, the quantitative and qualitative ingestion and assimilation, and finally their metabolism. It happens, as well, that this aspect of nutrition has exceedingly important relationship with the maintenance of a state of health. The normal physiologic processes of growth, development, and resistance to disease are materially affected by disturbance of these elements.

It is because of such circumstances that dental caries is frequently a very sensitive indicator of nutritional maladjustment. Moderate or subclinical disorders lacking in sufficient degree or duration to furnish the more obvious, clear-cut manifestations of disease may be, and frequently are, registered by lowered caries resistance. The appearance of carious lesions and the determination of active caries susceptibility by modern methods deserves careful attention from this point of view. It can be said without hesitation that the child with severe active caries is in a state of health which, if continued, provides a hazard from other and more serious pathologic conditions. For these reasons, entirely aside from its purely dental significance, the disease is deserving of further investigation from a pediatric point of view.

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DR. HAWKINS.—Inasmuch as Dr. Noyes has dwelt with considerable detail upon the incidence, etiology, symptomatology, and pathology of dental caries and touched only lightly upon the subject of treatment, it will be well if I enlarge upon this latter phase of the subject.

In a discussion of treatment considerable space could be given to operative technique and filling materials. Such a discussion might be of interest to the dentist but would be of little value to the pediatrician. Before leaving the subject of fillings it would be apropos to state that it is extremely desirable to fill all cavities in the child's teeth as soon as possible, and if the teeth are lost or missing, to hold the space by "space retainers" so there will be sufficient room for the permanent teeth to erupt. Cavities often develop as early as the second year, and it is perfectly feasible for a dentist who specializes in children's dentistry to fill such teeth at that age.

Preventive dentistry has been a challenge to the dental profession for quite a number of years. The response to this ideal has taken many directions. One group has endeavored to stress the value of oral hygiene; another has stressed the filling of cavities while they are small so there will be little danger that the pulp will become involved. Another group favors filling all faulty pits and fissures before a cavity has actually developed. Others see orthodontia as a preventive technique. Some have endeavored to destroy the aciduric bacteria in the oral cavity by mouth washes and antiseptics; still others have endeavored to change the body chemistry by foods and glandular preparations.

Of the different methods suggested above for the prevention or arresting of caries perhaps oral hygiene has been given the most widespread demonstration over a period of years. As a means of controlling dental caries in society as a whole it has been very disappointing. There has been no appreciable lowering in the

incidence of decay in the United States in the past twenty years. For fear of creating a misunderstanding I feel I can say the dental profession still feels the tooth brush is a helpful agent in controlling caries in isolated individuals as well as helpful in maintaining gum tone and mouth cleanliness. Few dentists today feel that the tooth brush will ever seriously lower the national incidence of dental decay.

There are two techniques that are challenging the dental profession today. I refer to the filling of faulty pits and fissures before decay takes place and to the control of decay by maintaining normal body chemistry which usually means a definite nutritional program. The reports that are being received indicate that the filling of faulty pits and fissures is a helpful procedure in many cases. Just how far this method can go in lowering the national incidence of caries only time will tell.

According to Dr. Thaddeus P. Hyatt about 60 per cent of all cavities occur in tooth surfaces containing pits and fissures and about 40 per cent of caries occur on the smooth surfaces of teeth. Even if all caries could be prevented on surfaces containing pits and fissures, which we know is not possible, we would still have a sizable percentage of caries not under control by this technique. We are therefore driven to look beyond instrumentation as a means of controlling caries.

The biochemical technique which rests on nutrition and the endocrine balance seems to me to offer more promise for the future than any other technique or method so far proposed. In any technique which endeavors to arrest or prevent caries by a change in body chemistry we have this also to consider: Will the general health likewise be benefited? The reports seem to indicate that when mouth health is secured general health is improved. This is naturally what would be expected as it is not consistent to assume the changes that would secure good health in one part of the body would be conducive to ill health in another. Inasmuch as dental decay can occur before clinical signs of a general disturbance can be seen, it would appear that dental caries could be used as an index of certain failures in the body chemistry.

In approaching the control of dental caries by biochemical means it will be necessary to review briefly the etiology of this condition if we hope for a rational technique. The etiology of caries can be divided into two divisions: the inciting factors and the predisposing factors. There is little or no dispute over the inciting factors. Miller's theory is still accepted by the majority of research groups. It is briefly this: the aciduric microorganisms working on the carbohydrates, principally cereal starch, develop enough acidity to cause the decalcification of the tooth. Any other acid can also cause decalcification. We find some individuals who are subject to regurgitation will develop a type of caries; also those taking hydrochloric acid by mouth can develop decalcification. We see from time to time caries resulting from highly acid candies like lime drops used continuously over a long period of time.

While research groups are very much agreed on the inciting factors, the predisposing factors have caused considerable controversy. I personally feel that there is not as much confliction as may appear on the surface. We are looking at a problem that has many angles; some are very important while others are minor. The picture is being put together slowly. I will briefly name the elements that have been suggested as having a definite bearing or influence on the underlying factors: the calcium-phosphorus balance, the acid-base balance, the ptyalin activity of the saliva, the amount of carbohydrates, especially cereals, in the diet, vitamins A, B, C, and D, the hydrochloric acid level, the iron level, the pancreatic and liver function, the basal metabolic rate, and a number of others.

Every one of the above elements or factors I believe can be shown to influence directly or indirectly the susceptibility of an individual to caries. It might not seem that all of these are related to dental caries but I believe a little study will reveal that they are so related. If acids in the mouth cause dental decay the only way to eliminate these acids is by dilution or neutralization. The neutralizing fac-

tors can be divided into those that readily ionize and those that do not. Those that ionize can be measured by electrical titration or any other equivalent method. The most important neutralizing element in the saliva that does not ionize is calcium. This can be measured by standard techniques. The total ionizing and un-ionizing factors that can combine with an acid constitute the buffer value. The total buffer value of the saliva is what confers the principal immunity to dental decay.

We have established one other factor that is important in the control of caries and this is the ptyalin activity of the saliva. If the residual starch in the mouth is not converted to dextrin or sugar it is acted upon by the aciduric microorganisms in the mouth and converted into an organic acid, possibly lactic. Those mouths that are deficient in ptyalin are as a rule slightly more susceptible to caries than those with a normal level. We have been measuring the ptyalin level for about a year and a half and are satisfied it is a definite factor in caries.

The total level of the minerals like calcium, phosphorus, potassium, sodium, etc., the vitamin levels and the glandular and endocrine functions constitute the factors that help maintain the buffer salts and give the principal immunity to dental decay. We have worked with this problem for over sixteen years. For some time we have included the following tests in our routine check on the saliva and urine: the buffer value, potassium, calcium, chlorine, phosphorus, vitamin C, and the ptyalin activity on the saliva alone. We make the usual laboratory tests on the urine. The stool is checked for hydrogen-ion concentration and occult blood. A hemoglobin test is made. A rough estimate of the basal metabolic rate is secured by aid of the pulse, temperature, and blood pressure.

In the control of dental decay we feel the most important relationships are the calcium-phosphorus balance and the acid-base balance. As a rule the influence of ptyalin on caries is not as important as those relationships mentioned above. The ptyalin level of the saliva is at times an important factor, however, especially when cereals are high. The percentage of refined cereals in the diet is important as the level of ptyalin rapidly falls on a high intake.

Our tests seem to indicate that the ptyalin of the saliva, the amylolitic serum enzymes of the blood, and the amylolitic power of the external secretion of the pancreas are one and the same and are increased or decreased by the percentage of vitamin B_1 or better still the vitamin B complex in the diet. Hence, when vitamin B is low the ptyalin is low and a greater tendency to caries is present. Dr. Weston A. Price has called attention to the fact that the incidence of decay is much higher on a refined cereal diet than on a similar diet containing unrefined cereals.

Most of the other factors mentioned as influencing caries, as the vitamins, hydrochloric acid, iron, pancreatic and liver function, and basal rate, do so as they increase or decrease the assimilation or level of the important factors involved.

The proof of any system or technique is how it works out in practice. A controlled demonstration on one hundred children for over two years showed only one cavity of decay developing. Our office records show that decay is being stopped in 95 per cent of all children and 85 per cent of all adults under my care. Such results are a challenge and demonstrate conclusively that dental caries is a condition controllable through biochemical means.

DISCUSSION

DR. JOSEPH PALMA (HONOLULU).—At what period in gestation do the tooth buds appear? Does the general physical condition of the mother at this time affect their development? In my experience, we see little trouble with the teeth in children whose mothers were supervised during pregnancy and kept on a simple diet.

CHAIRMAN NOYES.—Swelling along the dental lamina appears at the end of the second month (21 mm. embryos). Clearly defined tooth buds are developed

by the end of the third month. Calcification of the deciduous teeth begins in the fifth month of intrauterine life and may be demonstrated in the tooth buds of the first permanent molars a few weeks after birth. The general physical condition of the mother may affect both the growth and calcification pattern of her baby's teeth, but the degree and perfection of calcification are more readily altered than the growth pattern. If there is poor mineralization of the teeth at birth, the spread of caries is more rapid. Local factors, however, are most important in the production of the lesions. There is deficient mineralization in rickets, yet the hypoplastic teeth of rachitic children do not appear to be more susceptible to caries.

DR. H. H. RAY (San Mateo, Calif.).—Dr. Noyes, will you amplify your remarks about the relation of conditions in pregnancy and the teeth of the infant?

CHAIRMAN NOYES.—In a study of five hundred supervised pregnant women in Germany, the incidence of caries was found to be only slightly greater than in nonpregnant women. During lactation the incidence of caries is just as great or greater. I feel that more blame is placed on pregnancy per se than is warranted. In any event the caries of pregnancy is not due to demineralization of the teeth but to changes affecting the oral flora. With respect to the infant, the toxemias of pregnancy may affect the formative cells of the teeth; vitamin A deficiencies have been reported to affect the growth pattern, and nutritional disturbances, the quality of calcification. The structure of the tooth influences the rate at which it is destroyed, while later environmental conditions determine the activity of the decalcifying organisms.

DR. HAWKINS.—Our studies of calcium in the saliva show that calcium diminishes as pregnancy progresses. After delivery the calcium returns to normal. With the onset of lactation calcium values decrease.

DR. E. E. MOODY (Los Angeles).—Do you mean that actual calcium values in the blood are decreased or do you refer to saliva studies only?

DR. HAWKINS.—I refer to saliva values only. From our studies in patients with 10 mg. of calcium per 100 c.c. of blood we may find a saliva content of 30 mg.

DR. RAY.—Do you advise local or general treatment?

DR. HAWKINS.—I advise control of acidity in the mouth. We have found that as acidity of the saliva increases, the urine becomes alkaline.

DR. MOODY.—Does the amount of calcium in the urine fall as the calcium increases in the saliva?

DR. HAWKINS.—It does. Two factors bring this about. In high fat diet, elimination of calcium by bowel is increased. We must also pay attention to the potassium level which, if increased, promotes the elimination of calcium through the kidney.

DR. W. W. BELFORD (San Diego, Calif.).—Is dental caries the same process, regardless of age?

CHAIRMAN NOYES.—Essentially, yes. The question is not one of age, but rather of the presence of acidogenic organisms, the length of time of exposure, concentration and confinement of acid, and the resistance of the host. These factors may vary at different ages.

DR. MOODY.—Does the feeding of calcium overcome the susceptibility to caries in the pregnant woman?

CHAIRMAN NOYES.—Where the vital contributive factor is lack of mineral it may be very helpful, but it is not a panacea. Decay proceeds from the outside of the tooth. It is more likely to be the environment which is at fault, rather than

the tooth itself. The condition of the mouth, the presence of causative organisms, and the physical condition of the woman may all affect the environment of the teeth. We may try to improve the local environment by giving milk, or in case milk is not well handled, by giving calcium and phosphorus. However, mineral is often inadequate in the dosage usually given. The addition of vitamin D and B is helpful. Frequently we can favorably influence caries by increasing protein intake and decreasing carbohydrate.

DR. A. J. THORNTON (SAN DIEGO, CALIF.).—How do you explain caries in a tooth at the time of eruption?

CHAIRMAN NOYES.—A defect in calcification may simulate caries. True caries does not occur before the exposure of the tooth in the mouth.

DR. BEULAH WELLS (CLEVELAND).—Does rubbing teeth through the gum do harm?

CHAIRMAN NOYES.—Where there is much fibrous tissue in the overlying gum, it is a legitimate procedure. However, it is possible to introduce infection in this way into the tooth crypt. The general condition of teething may predispose to altered mouth conditions, affect digestion, and in turn the general condition of the infant; thus, in cases where there is prolonged irritation due to teething the practice may be justified. It should be used with discretion.

DR. WELLS.—Is a carious tooth of the first dentition better than none?

CHAIRMAN NOYES.—A carious tooth is always a potential hazard, opening the way to infection of the dental pulp with pathologic sequelae. On the other hand, extraction of a tooth may affect position of adjacent teeth and also the teeth in the opposing jaw causing an orthodontic problem. The cavity should be filled. If the tooth must be sacrificed to eliminate focal infection, the integrity of the dental arches may be preserved by space maintainers in the first dentition and bridges in the second.

DR. JAMES DUNN (DAVENPORT, IOWA).—What do you think about oatmeal and other cereals in the diet of the child?

DR. HAWKINS.—I prefer potatoes and bananas. I wonder if we have the right to feed starch to very young children. In my opinion they do not develop the full power of starch digestion until they are 3 years old.

DR. ANN L. MARTIN (HAYWARD, CALIF.).—Are you hostile to candy and sugars?

DR. HAWKINS.—Sugar satisfies caloric needs before the mineral requirement is obtained. Therefore, in my opinion, weight is not to be thought of so much as good nutrition.

CHAIRMAN NOYES.—*High* cereal and sugar feeding have a definitely undesirable effect. This raises some, as yet unanswered, questions. It is due to what occurs in the mouth? Is it due to the bacterial flora which is developed? Is it due to changes in the relative alkalinity of tissue fluids? Is it due to the effect on mineral metabolism?

DR. MOODY.—What is the significance of white patches on children's teeth?

CHAIRMAN NOYES.—They are often poorly calcified areas. In the presence of active factors they may become sites of caries, but in themselves they have no relation to caries.

DR. H. F. HELMHOLTZ (ROCHESTER, MINN.).—Is it definitely accepted that dental caries is a bacterial disease?

CHAIRMAN NOYES.—Yes, it is pretty generally accepted, but not without some question.

DR. HELMHOLTZ.—What conditions do you try to achieve in regulating the diet?

DR. HAWKINS.—Normal values of calcium and phosphorus in the urine, saliva, and stool. The normal saliva has a pH of 7.6; potassium of 100 mg. per 100 c.c.; chlorides 90 mg. per 100 c.c.; calcium of 37 mg. per 100 c.c.; phosphorus of 60 mg. per 100 c.c.

The normal urine has a pH of 6.2; potassium of 150 mg. per 100 c.c.; chlorides of 270 mg. per 100 c.c.; calcium of 10 mg. per 100 c.c.; phosphorus of 60 mg. per 100 c.c.

DR. HELMHOLTZ.—Do you adjust the diet of the individual?

DR. HAWKINS.—Yes.

DR. H. F. DIETRICH (BEVERLY HILLS, CALIF.).—If caries depends on accumulation of starch in the mouth, why wouldn't mechanical cleansing two or three times a day prevent caries?

DR. HAWKINS.—One cannot clean the mouth any more than you can render the mouth sterile.

CHAIRMAN NOYES.—There is another factor aside from mechanical cleansing. High starch (or other carbohydrate) in the diet may affect the saliva which in turn affects the flora.

DR. HELMHOLTZ.—Can you give the details of making cultures from the mouth?

CHAIRMAN NOYES.—The procedure we have been utilizing is as follows: a specimen of saliva is stimulated by chewing of paraffin, collected, and forwarded to the laboratory for plating. I cannot give the culture media and details of technique now in use.*

DR. HAWKINS.—How does Dr. Bunting control the *Bacillus acidophilus?*

CHAIRMAN NOYES.—I dislike to answer for Dr. Bunting, but I understand that he eliminates carbohydrates.

DR. HELMHOLTZ.—Several years ago, I made a survey in the rural districts of Georgia. In one small school for colored children, I found twenty-three out of twenty-four with perfect teeth. Upon questioning, I found that they were getting a diet of buttermilk, corn bread, pork grease, a few greens and very little other carbohydrates.

CHAIRMAN NOYES.—It may be significant that this diet is low in sugar and starch. In England during the war, there was less caries than later. This was thought to be due to less sugar consumption during the war. We have been able to produce

*The following is supplemented by statement from the Department of Therapeutics, University of Illinois College of Dentistry, to whom the salivary samples are forwarded: Salivary samples are poured within an hour in plates of tomato agar pH 5.2 (similar to that used by the Michigan group). Plates are made in the following dilutions: 0.1 c.c. of saliva, 0.1 c.c. of 1:100 saliva, 0.1 c.c. of 1:1000 saliva. Incubation at 37° F. and readings made at two and five days.

caries in students previously immune by putting them on a high candy diet. The reaction of the individual to his diet may influence caries as well. In general, children on good diets have little caries. Where they are indulged they are apt to develop extensive caries.

DR. G. D. C. THOMPSON (PORTLAND, ORE.).—Are there factors in early life that might cause caries later on, such as a poor diet in early life but a good diet later on in life?

DR. HAWKINS.—One has to maintain a good diet. Immunity may be lost in a few months.

CHAIRMAN NOYES.—Early deficient diet may affect tooth structure (the importance of this factor was discussed previously) which would appear to give it a very minor role in later caries production, unless one considers the possibility of a disturbance of sufficient severity to produce sustained effect on other tissues—cardiovascular damage for example.

DR. C. G. ASHLEY (PORTLAND, ORE.).—Why do some have poor deciduous teeth and good permanent teeth?

CHAIRMAN NOYES.—While the deciduous teeth have less enamel to penetrate permitting deep cavitay formations upon less protracted periods of attack, the principal factor lies in changes in the oral environment between the ages of the deciduous and permanent dentitions effecting alterations from relative susceptibility to immunity or the reverse, depending upon the vicissitudes of the individual.

DR. HAWKINS.—Insufficient calcium to go around during rapid growth periods may be a factor.

DR. ASHLEY.—Is there a metabolic factor during adolescence?

CHAIRMAN NOYES.—Possibly, as suggested by the reports that hypothyroid children are more susceptible to caries. There is no uniformity of opinion among investigators. It is probable that the increased caries of adolescence is related to metabolic changes if metabolism is considered broadly to include the tissue demand for particular food substances, as well as their reaction to them. The numerous contributory factors to caries susceptibility mentioned may be affected by systemic changes. The oral flora may be affected by a change in the use of a diet previously satisfactory, by changes in the cellular activity concerned with the assimilation of food, utilization of food or secretory activity of the tissues supplying oral fluids. On the other hand, the adolescent period may create an appetite which alters the proportions of food elements supplied as well as their subsequent utilization.

DR. HAWKINS.—One can see an increase in the calcium level of the saliva in two weeks' time upon giving hypothyroid children thyroid extract.

DR. V. E. STORK (LOS ANGELES).—Is there any evidence that calcium taken by mouth can change the character of the enamel already formed?

CHAIRMAN NOYES.—Some think so, by circulation through the dental tubules or diffusion through the enamel. The latter is doubtful and must be extremely slow if it does take place. Others believe that mineral salts of the saliva may be precipitated in porous enamel. There are a few who feel that actual carious cavities will heal and fill up. I have never seen it. The administration of calcium, in calcium-deficient individuals, may affect the saliva and in this way influence dental caries. Its use has been overemphasized in the past.

Secretaries,

ROBERT E. RAMSAY, M.D., Pasadena, Calif.

E. H. CHRISTOPHERSON, San Diego, Calif.

Academy News

Dr. John Signorelli, New Orleans, who had just been designated state chairman for Louisiana, died Tuesday, December 13, 1938. He was Professor of Pediatrics of the Medical School of Louisiana State University.

Dr. Russell Sturgis Rowland, one of the early Fellows of the Academy of Pediatrics, died at his home in Detroit, Sept. 29, 1938, after an illness which had made him a partial invalid for many years.

After graduation in medicine from the University of Michigan and interneships in the Boston City and Boston Children's Hospitals, Dr. Rowland came to Detroit in 1903 to be one of the pioneers in specialized pediatric practice in that city, and rapidly developed a large and devoted clientele. He was a careful, conscientious practitioner and an excellent clinician; in consequence he was recognized throughout his career as a leader in his chosen field. He was prominent also in the early development of child welfare work in the city and its environs.

Personally, he was honest, simple, straightforward and very likable—a good friend with no enmities. With a strong taste for rural life, he made hobbies of gardening and birds and maintained a small farm.

A few years after the War there came into Dr. Rowland's hands a patient with a striking type of the Schüller-Christian syndrome, then little known. His clinical acumen led him to perceive the possible significance of this condition in relationship to other disorders of lipid metabolism, and from that time on he devoted a large part of his time to the study of these diseases, obtaining and correlating information from all over the world, and becoming ultimately the recognized authority on the subject and author of sections dealing with it in several leading systems of medicine. His alma mater recognized his achievements by conferring upon him the honorary degree of M.Sc., and he was given a medal by the American Medical Association for a scientific exhibit of his material. His work in this field constitutes one of the outstanding examples of the possibility of first-rate clinical investigation by a man whose chief activity lay in a busy private practice.

To Dr. Rowland is attributed a large share in the development of pediatrics in Detroit and Michigan and in the furtherance of higher scientific ideals in all branches of medicine.

The Ninth Annual Meeting of the Academy will be held at the Netherland-Plaza Hotel, Cincinnati, Ohio, Nov. 16, 17, and 18, 1939.

Region I will hold its next meeting at the Waldorf-Astoria Hotel in New York on June 1, 2, and 3, 1939.

Region II will meet Monday and Tuesday, May 15 and 16, 1939, at Memphis, Tenn.

Dr. George F. Munns, Winnetka, Ill., has been appointed chairman, and Dr. John S. Bigler, Highland Park, Ill., secretary of the Committee on Hospitals and Dispensaries.

News and Notes

The E. Mead Johnson Award for Research in Pediatrics

At the Eighth Annual Meeting of the Academy in 1938, the offer of Mead Johnson & Company to establish the E. Mead Johnson Award for Research in Pediatrics for a period of ten years was accepted by the Academy. An academy committee on awards was appointed, consisting of Drs. Joseph Brennemann, Chicago; Irvine McQuarrie, Minneapolis; Oscar M. Schloss, New York; Edwards A. Park, Baltimore; and Borden S. Veeder, St. Louis (chairman). The committee announces the following rules and regulations governing the award.

1. Two awards, one of $500 and one of $300, will be given annually at the annual meeting of the Academy of Pediatrics.

2. The awards will be made for research work published during the previous calendar year.

3. There is no limitation as to the type or scope of the research except that it be in the field of pediatrics.

4. The award is limited to workers in the United States and Canada.

5. The award shall be limited to investigators who have been graduated not more than 15 years previous to the publication of the research.

6. There is no restriction as to the journal of publication of the research.

The Committee interprets 2 and 5 as follows:

The award in 1939 will be given for research published during the period Jan. 1, 1938, through Dec. 31, 1938, by a graduate of 1923 or later. The award in 1940 will be given for research published Jan. 1, 1939, through Dec. 31, 1939, by a graduate of 1924 or later, and so on for subsequent years.

Heads of departments and hospital services are requested to call attention to investigations meeting the requirements of the award and *in particular to research work in the field of pediatrics published in other than pediatric journals.* At present communications should be addressed to the chairman.

Communications in regard to the **American Academy of Pediatrics** should be sent to Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

Communications in regard to the **American Board of Pediatrics** should be sent to Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.

Considerable confusion and delay have been experienced because correspondents have confused the two organizations.

The Sixteenth Annual Meeting of **The American Orthopsychiatric Association,** an organization for the study and treatment of behavior and its disorders, will be held at the Commodore Hotel, Lexington Avenue and 42nd Street, New York, N. Y., on Feb. 23, 24, and 25, 1939. Dr. Norvelle C. LaMar, Secretary, 149 East 73rd Street, New York, N. Y.

Comments

IN "News and Notes" of this issue of the JOURNAL is an announcement of the E. Mead Johnson Award for Pediatric Research. This has been established by Mead Johnson & Company for a period of ten years, and is to be administered by the Academy of Pediatrics through a committee appointed by the Academy.

The award is given for the purpose of furthering the interest of younger investigators in the field of pediatrics, and hence the terms of the award require that it be given to graduates of fifteen years or less. The Committee in its selection, therefore, is not called upon to determine each year what it considers to be the most valuable or important contributions in the field of pediatrics, but simply the most valuable and stimulating contributions by younger investigators. The field of selection is distinctly limited by this restriction: for example, not a single article appearing in the recent Marriott Memorial issue of the JOURNAL is eligible for the award.

There is no limitation as to the scope of the research except that it be "in the field of pediatrics." Thus not only clinical research, but investigations in the field of biochemistry, physiology, pathology, psychology, public health, and all others are eligible provided the research is directly related to the field of pediatrics. Obviously this adds considerably to the work of the Committee, as the reports of such eligible research are frequently published in journals in special fields, as biochemistry. For this reason department heads, chiefs of hospital and laboratory services, and others in executive positions are requested to cooperate with and help the Committee by calling their attention to research eligible for the award, particularly investigations appearing in journals outside the strictly pediatric field.

It is hoped the award not only will serve as a concrete appreciation of the results of investigation, but will fulfill the purpose and desire of the donors of the award by serving as an incentive for research in pediatrics. Announcement of the recipients of the award will be made in the JOURNAL, and the award will be presented at the Annual Meeting of the Academy. Awards for work published in 1938 will be given at Cincinnati next November.